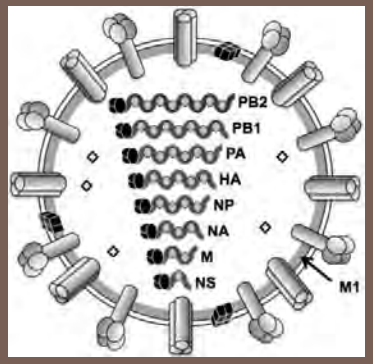
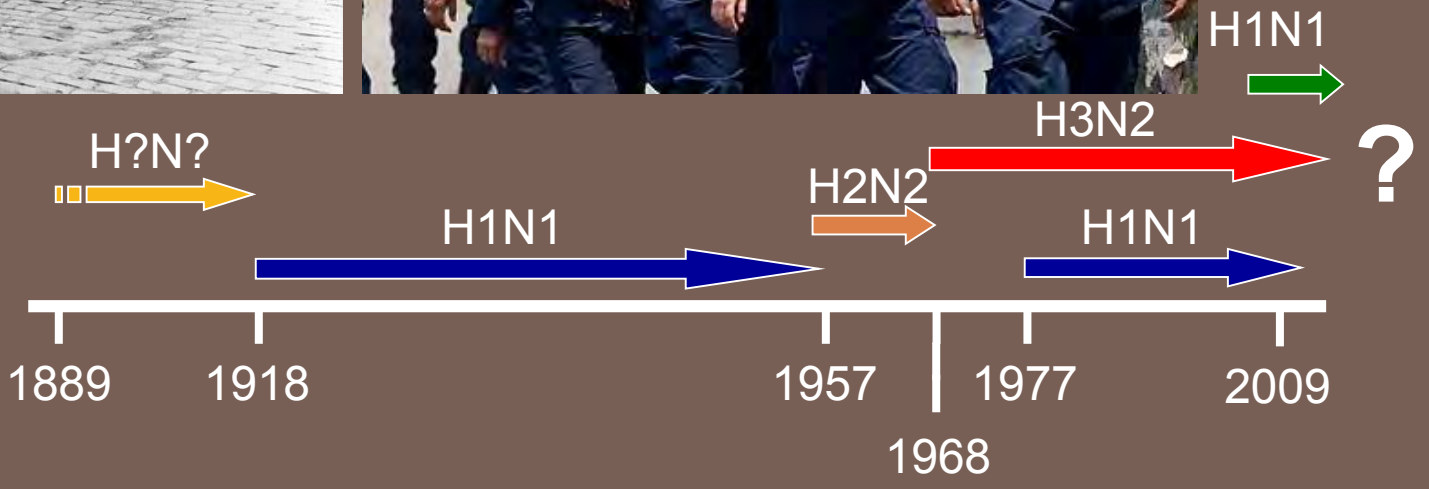
The Next Influenza Pandemic:
Remembering the Past & Planning for the Future





National Institute of Allergy and Infectious Diseases

Jeffery K. Taubenberger, M.D., Ph.D.

COMMENTARY

JAMA

May 9, 2007. **297**(18):2025-2027

The Next Influenza Pandemic

Can It Be Predicted?

Jeffery K. Taubenberger, MD, PhD

David M. Morens, MD

Anthony S. Fauci, MD

ALTHOUGH MOST EXPERTS BELIEVE ANOTHER INFLUenza pandemic will occur, it is difficult to predict when or where it will appear or how severe it will be. Neither is there agreement about the subtype of the next pandemic influenza virus. However, the continuing spread of H5N1 highly pathogenic avian influenza A (HPAI) among poultry on several continents, associated with an increasing number of severe and fatal human infections, has raised the pandemic stakes.[1] Genetically and antigenically divergent H5N1 HPAI strains appeared in 1997 and have been spreading globally since 2003.[2,3] To date, epizootics in approximately 60 countries have caused a reported 291 human cases with 172 deaths.[4]

reassortment with other avian influenza viruses.[5] It is not yet clear which of these changes is associated with lethality in wild birds or with pathogenicity and transmissibility in poultry and other species. Asymptomatic endemic H5N1 HPAI circulation in domestic ducks maintains a pool of pathogenic viruses to which poultry are continually exposed,[8] suggesting that the current H5N1 situation will likely persist.

There are limited data indicating whether any H5N1 influenza strain is evolving in the direction of human adaptation. Some H5N1 viruses exhibit a change in the polymerase protein complex PB2 that has been associated with increased H5N1 virulence in mice and ferrets, and adaptation of other avian influenza viruses to humans.[9-12] It remains unclear, however, whether this or any other mutation is associated only with increased mammalian virulence or provides an independent evolutionary advantage in birds.

The pathogenicity of influenza viruses for their different hosts is related to complex viral and host factors and re-

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COMMENTARY

No! (Not yet, at least)

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The Next Influenza Pandemic

Can It Be Predicted?

COMMENTARY

JAMA

August 12, 2009. **302(6)**:679-680.

Understanding Influenza Backward

David M. Morens, MD

Jeffery K. Taubenberger, MD, PhD

THE NOVEL 2009 INFLUENZA A(H1N1) PANDEMIC VIrus has been an unexpected trigger for pandemic preparedness plans in the United States and elsewhere.[1] It is appropriate to ask how the novel virus might behave epidemiologically in coming months, including the possibility of multiple recurrences or "waves." Spring circulation of the novel virus in the Northern Hemisphere at the end of the 2008-2009 influenza season inevitably has led to comparisons with events in 1918-1919, which in some settings were preceded and followed by outbreaks of respiratory illnesses. Some also believe that the 1918 pandemic began with a premonitory "herald wave," a term related to an old hypothesis, which influenza and dengue fever appeared to have supported, that as new viruses begin to circulate in human populations they inevitably acquire mutations that increase transmissibility and virulence.[2]

largely seasonal postpandemic influenza mortality peaks recognized in many large cities between 1890 and 1894.[7] What happened in 1918 was quite different. A recent tendency to refer to any influenza-like illness in the first 8 months of 1918 as "the spring wave" has altered the use of this term. Importantly, no viruses from the 1918 spring outbreaks or the summer wave have yet been identified. Many investigators working in and since 1918 have cited evidence for or against "spring waves" and their protection against later pandemic waves. However, such data are potentially confounded by inability to discern whether protection, or lack thereof, was associated with spring or summer infectious agents, which could have been different, and by the possibility of nonspecific short-term influenza cross-protection elicited by a different spring virus (had 1 or more circulated).

What is most puzzling is that during the 1918 pandemic, different countries had anywhere from 0 to 3 waves or occurrences, the course and timing of which varied greatly. Most of the world had 2 occurrences, one around October-

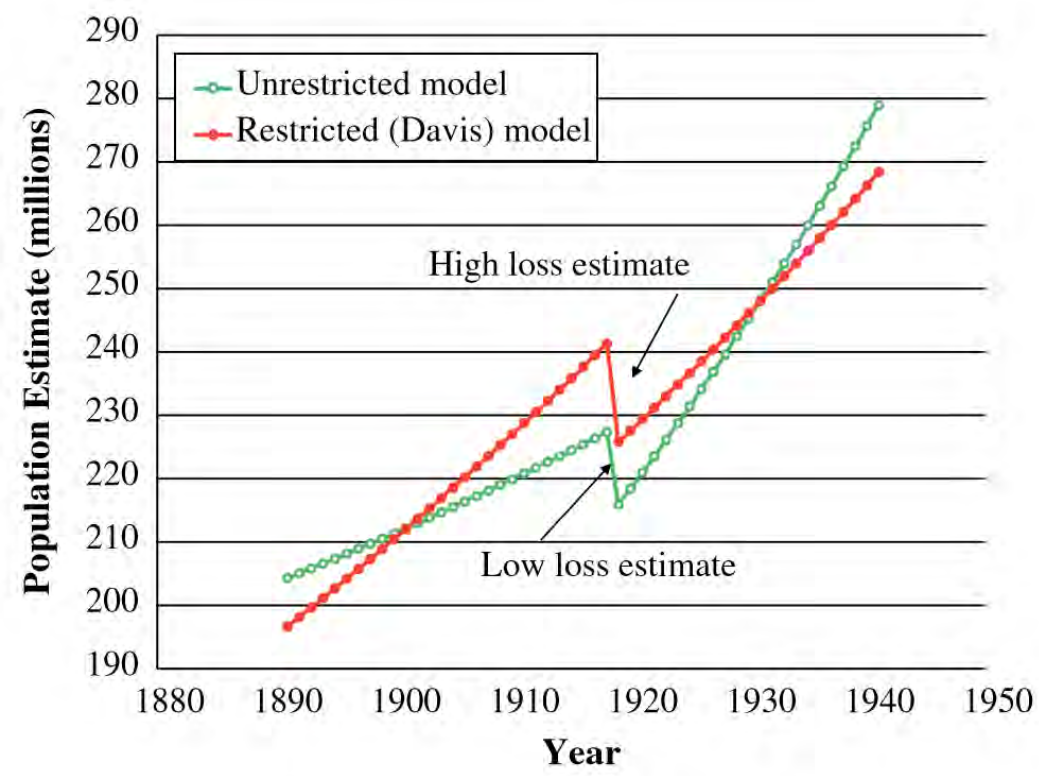
1918 Influenza Pandemic

1918 ‘Spanish’ Influenza Mortality

- Total global deaths in the 9 months of the pandemic in 1918-1919 estimated to be 50-100 million‡,*
- U.S. Deaths = 675,000
- Flu deaths in Philadelphia in October 1918 = 10,959. Total flu deaths = 15,785
- U.S. Military deaths to flu = 43,000 (out of ~100,000 U.S. Troop casualties in WWI)

‡Johnson NP, Mueller J. (2002) *Bull Hist Med* 76:105-15
*Perspective: ~37 million AIDS fatalities in the last 36 years

Global Influenza Mortality in 1918 Underestimated

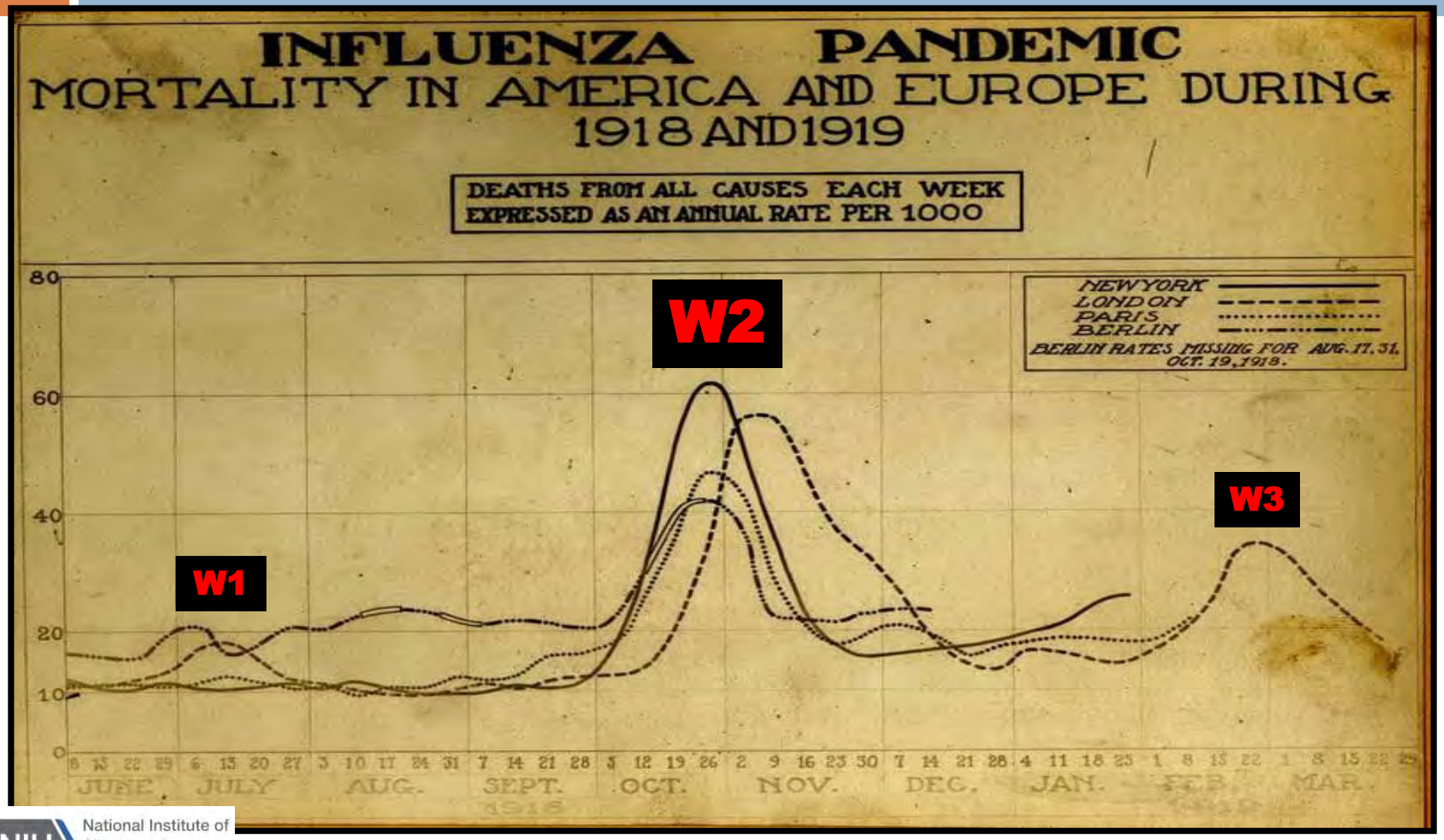


Studies of population size suggests that 1918 flu mortality in India was at least 14 million

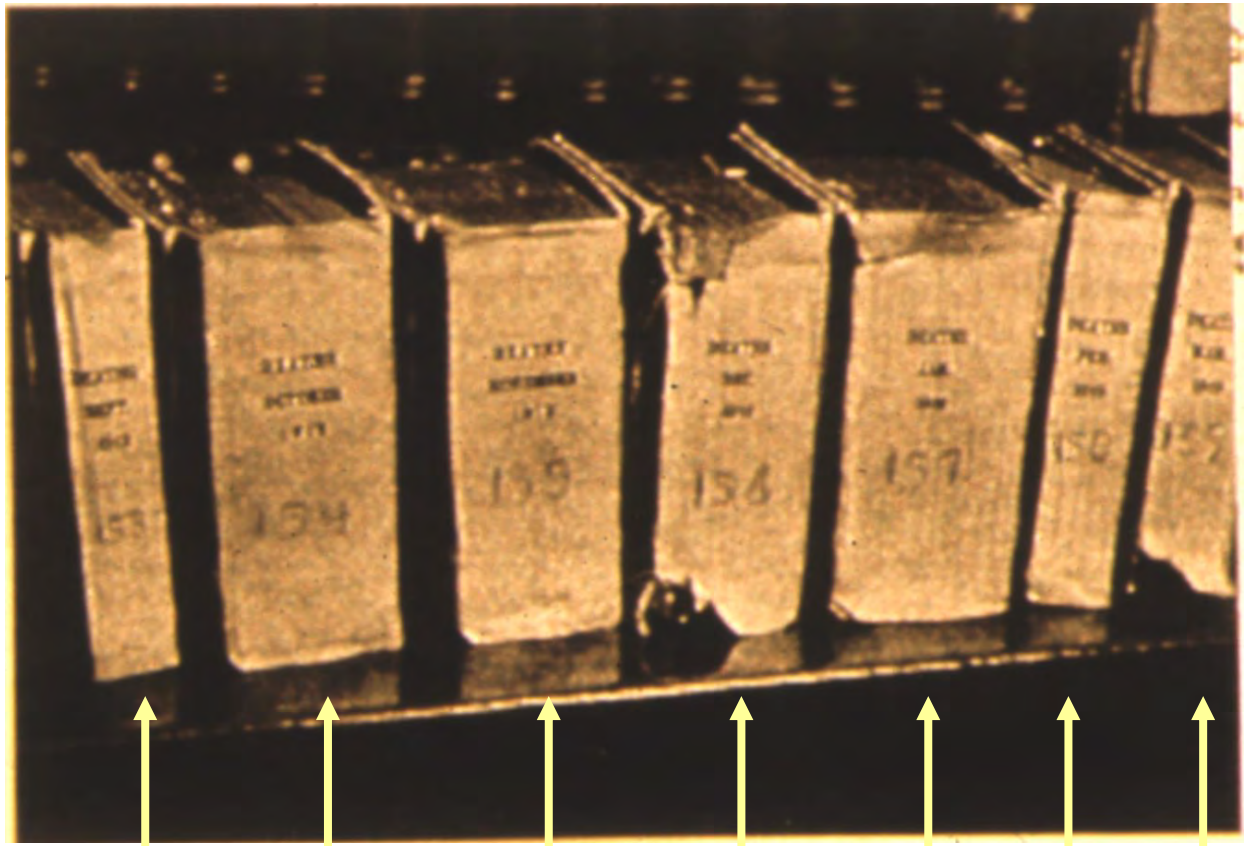
Chandra et al. *Demography* (2012) 49:857–865

US Soldiers with 1918 Influenza, Ft. Riley, KS

1918 Influenza Pandemic Waves

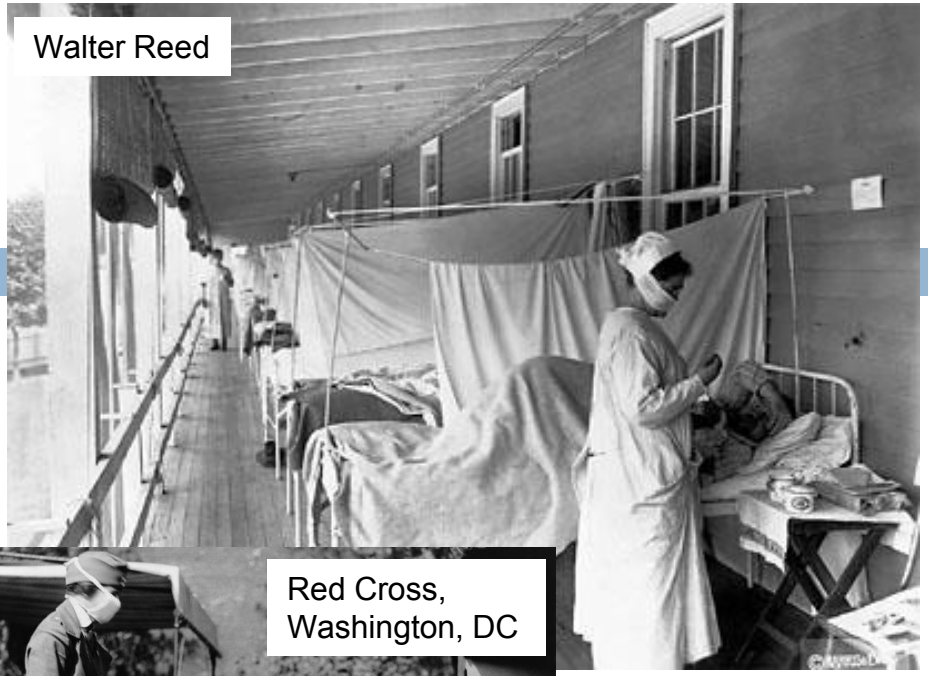


Death Registry, Oregon 1918-19

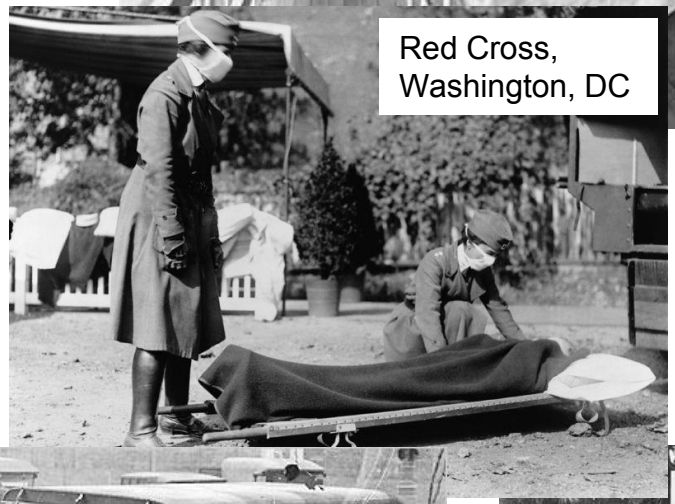


1918 Flu

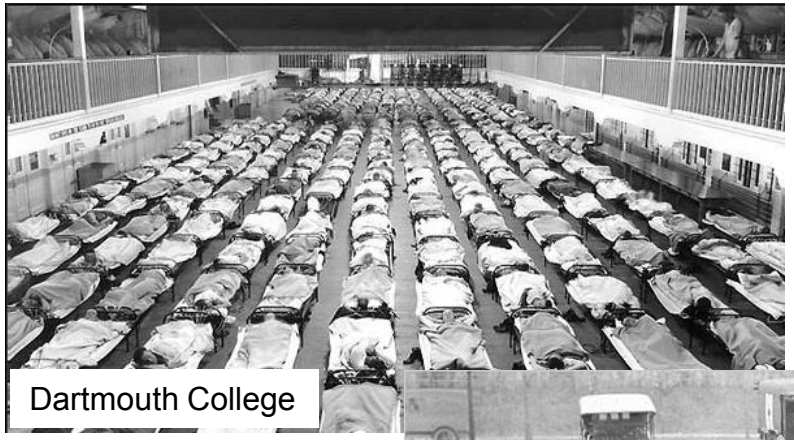
Camp Funston



Walter Reed



Red Cross, Washington, DC

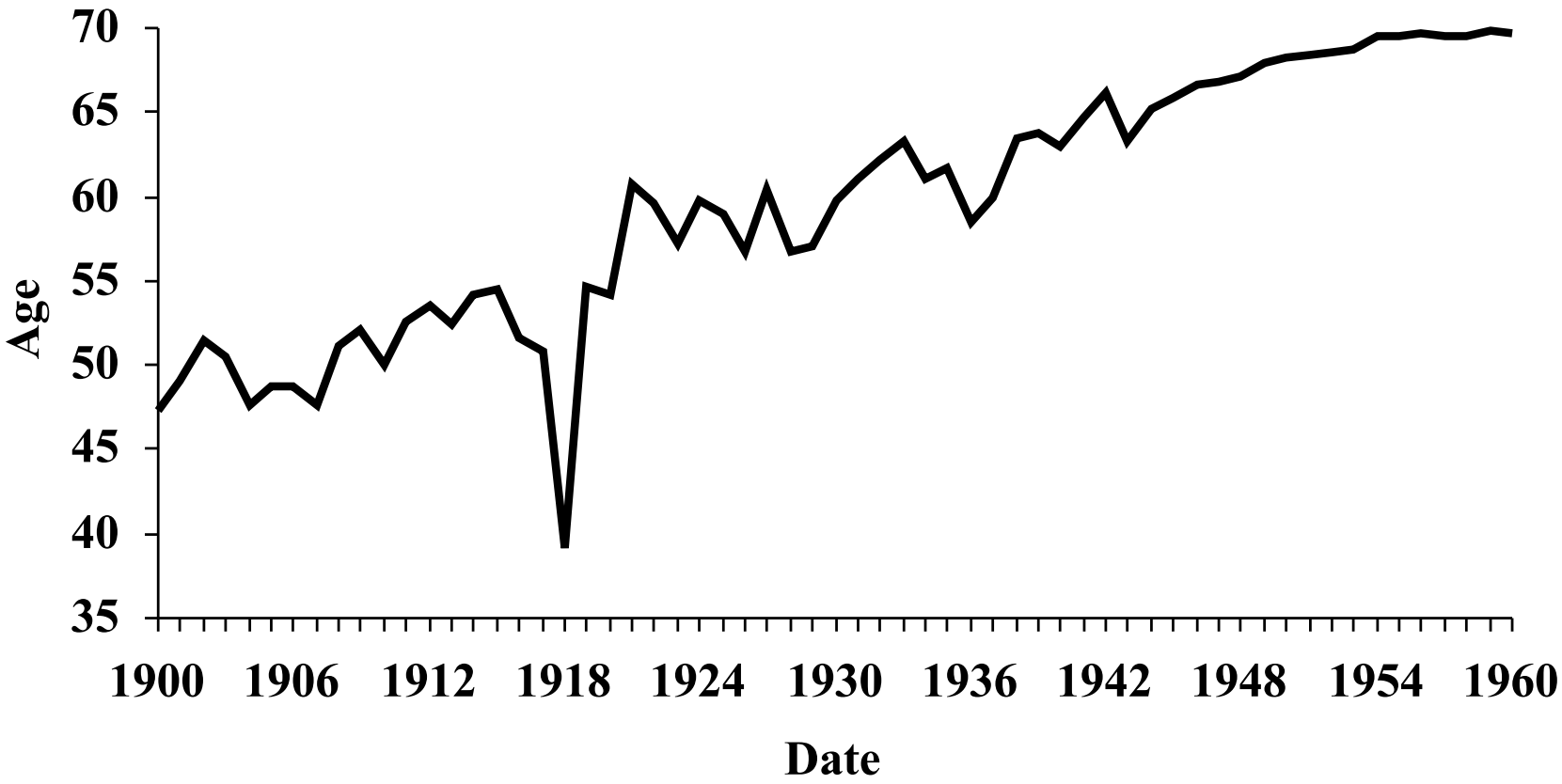


Dartmouth College

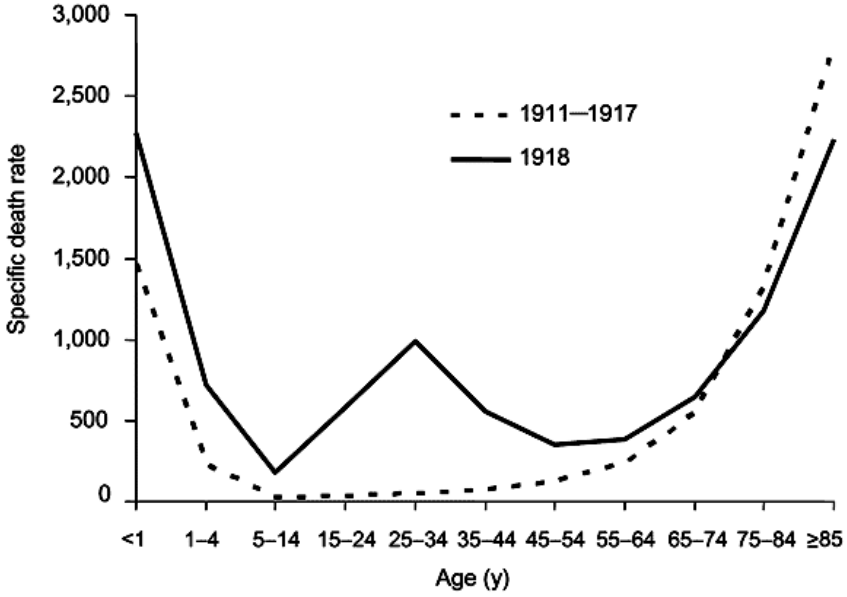
St. Louis

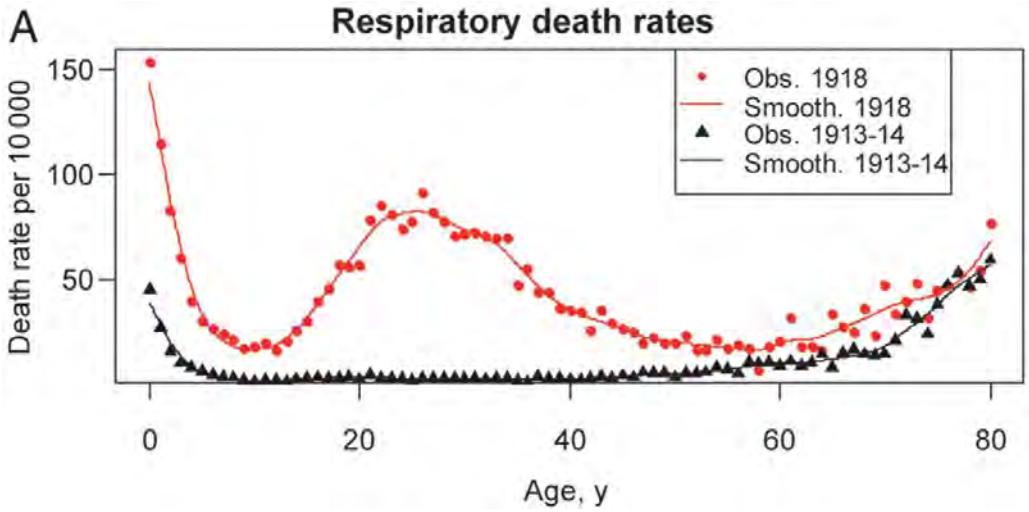
NIH National Institute of Allergy and Infectious Diseases

U.S. Life Expectancy 1900-1960



Unique 1918 Age-Specific Mortality





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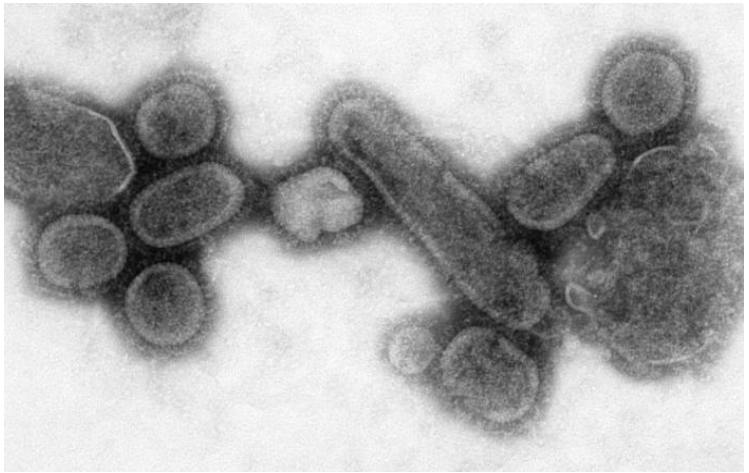
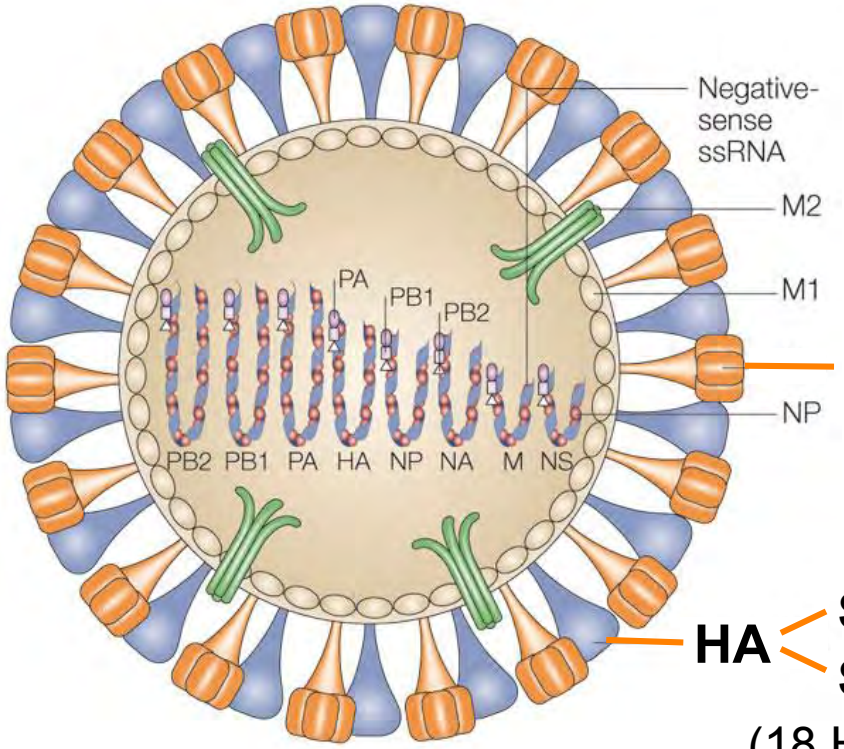
Viboud, *et al*. 2013 *JID* 207:721

Influenza A virus

- Family: *Orthomyxoviridae*
  - •Negative sense, segmented, single-stranded RNA genome
  - •8 segments, at least 12-13 ORF's





NA
(11 NA subtypes)

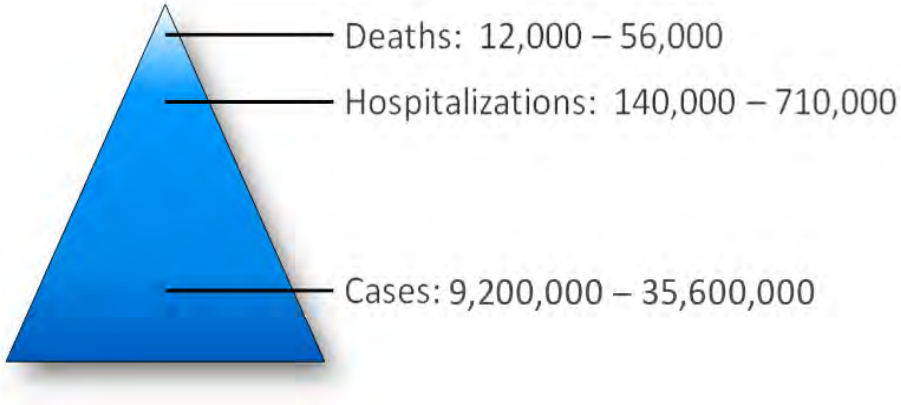
HA — **SAα2-6Gal**, **SAα2-3Gal**
(18 HA subtypes)

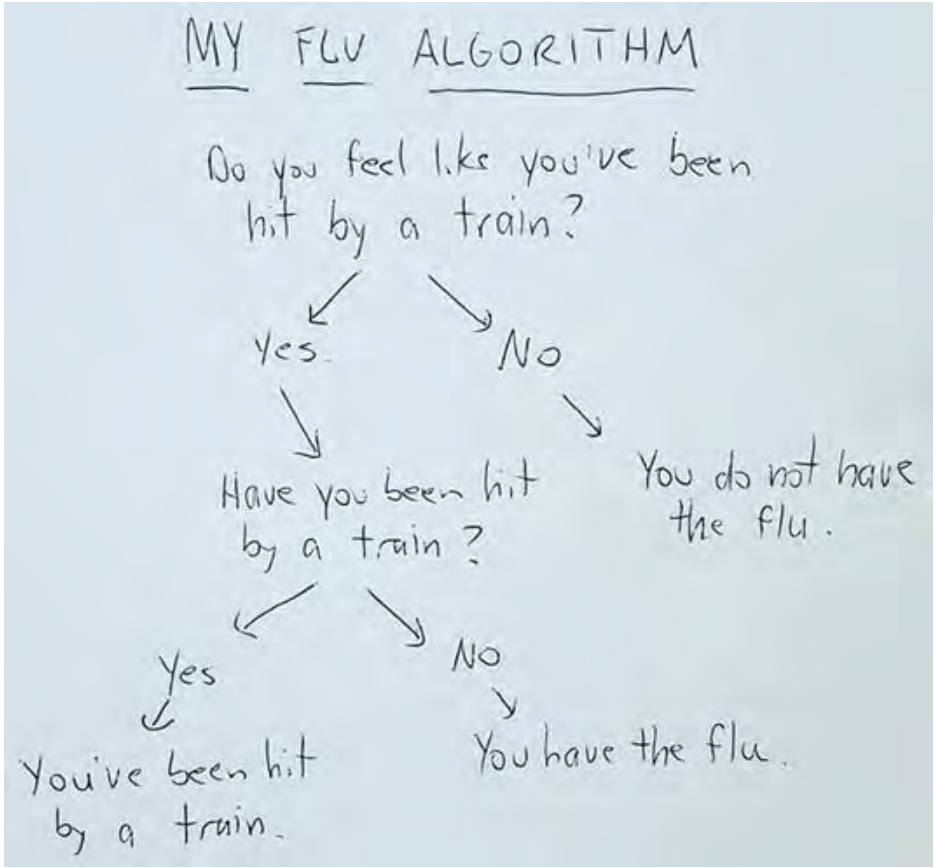
Modified from: Horimoto & Kawaoka (2005) Nat Rev Micro 3:591-600

"Shift and Drift"

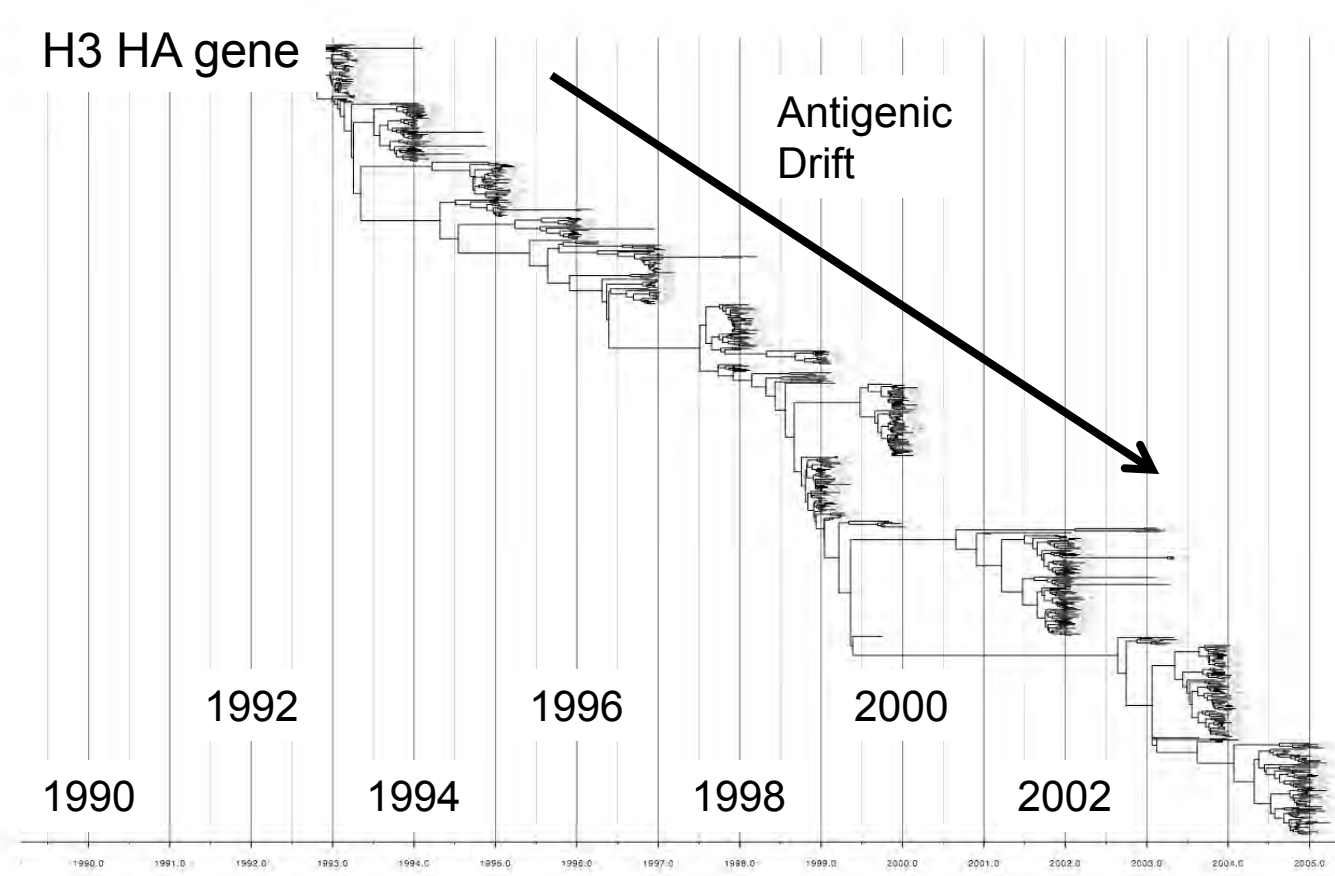
Influenza A viruses in humans

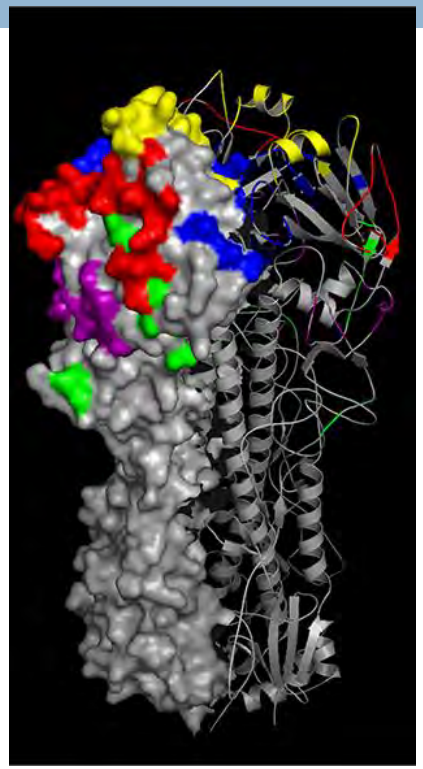
- Yearly outbreaks with up to 80,000 deaths in U.S.
- Occasional and unpredictable pandemic strains with increase in illness and death





Influenza virus evolution is extremely rapid



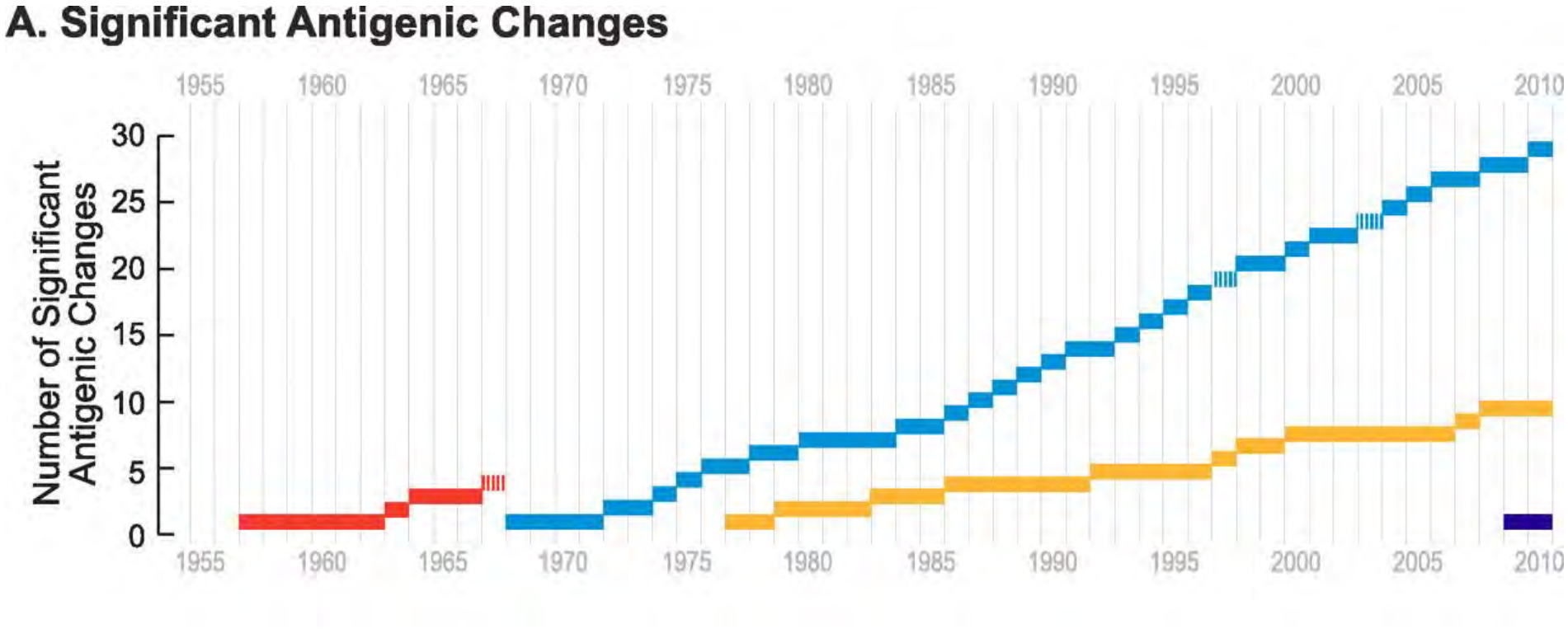


Antigenic Shift
(Intrasubtypic
Reassortment)

National Institute of Allergy and Infectious Diseases

Rambaut et al (2008) Nature 453:615-9

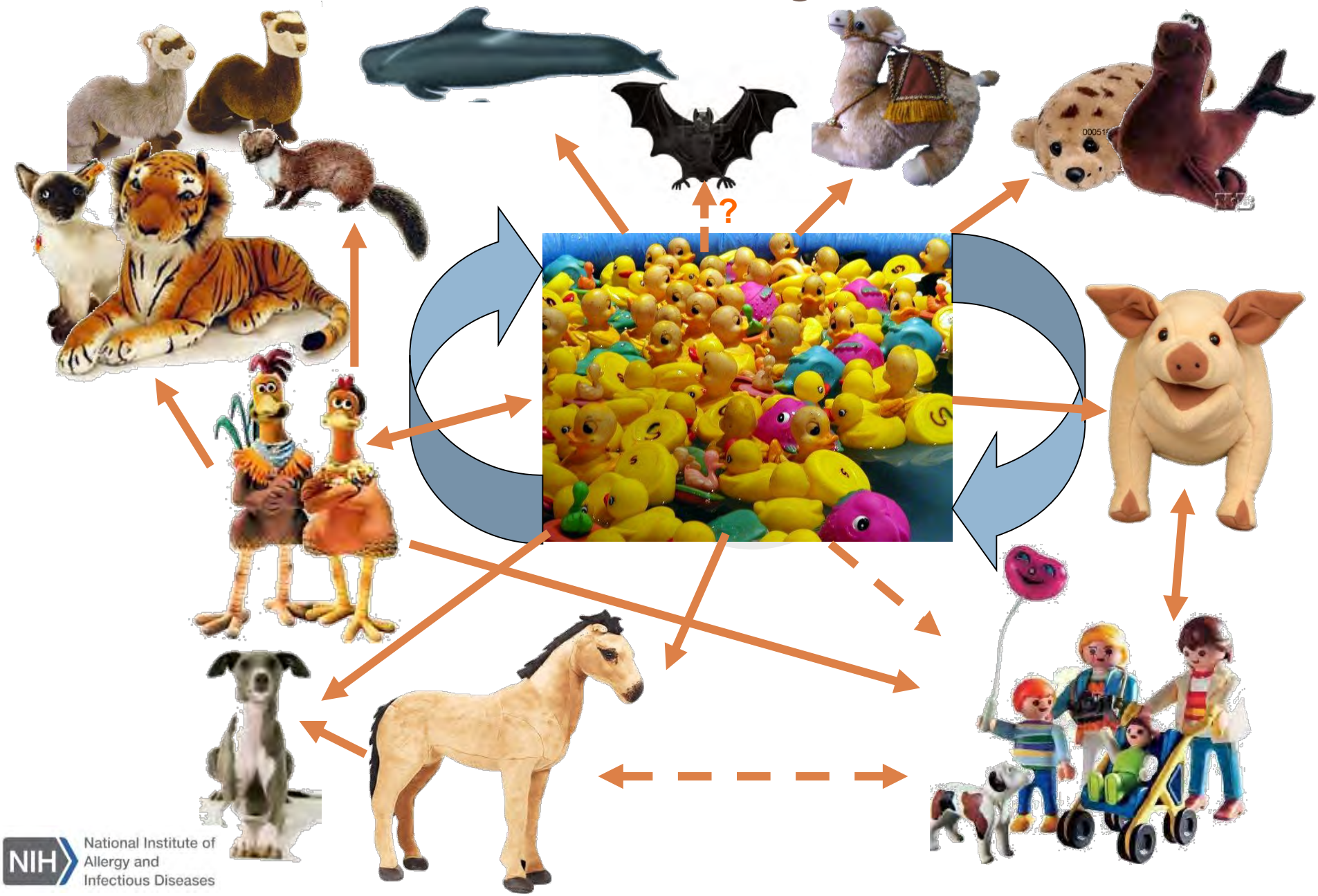
Antigenic Drift Necessitates Continual Updating of Annual Influenza Vaccine Strains



- Annual epidemic influenza causes up to 500,000 hospitalizations and up to 56,000 deaths in the U.S.
- Overall seasonal vaccine effectiveness over the past 10 years has ranged from 10 to 56%, with a mean of 40%, lower in at-risk populations

Morens & Taubeberger. mBio 2010;1:e00211-10

Influenza A Virus Host Range Quite Diverse



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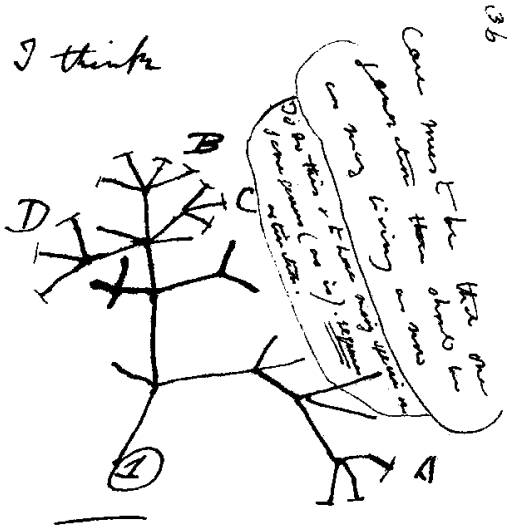
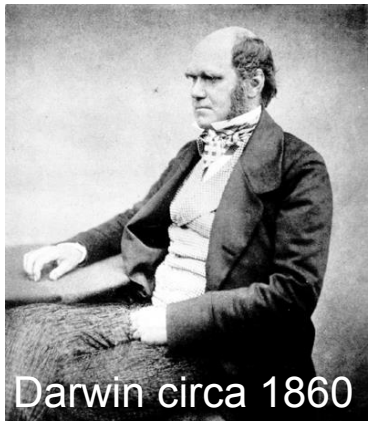
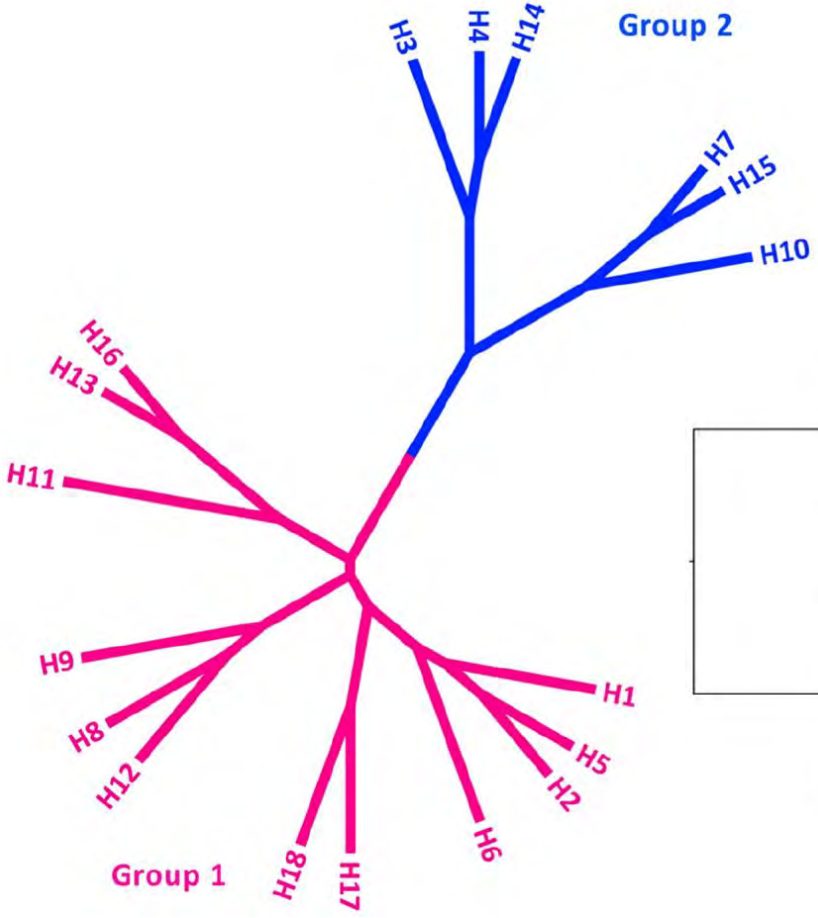
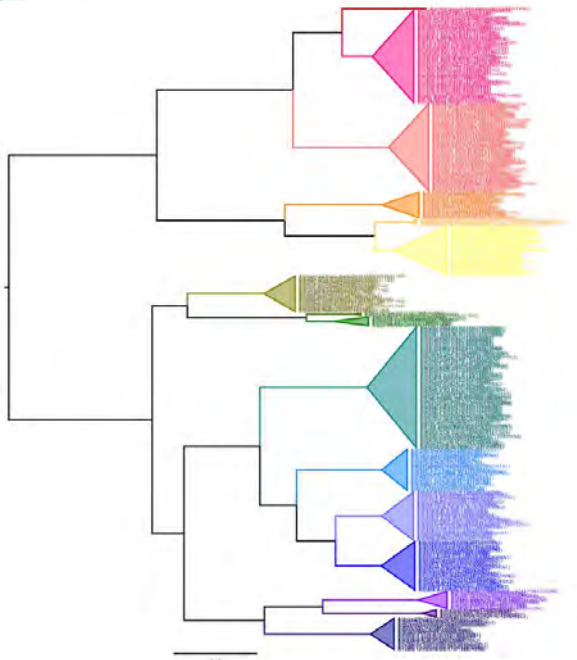
Avian Influenza A Virus Diversity




Darwin circa 1860





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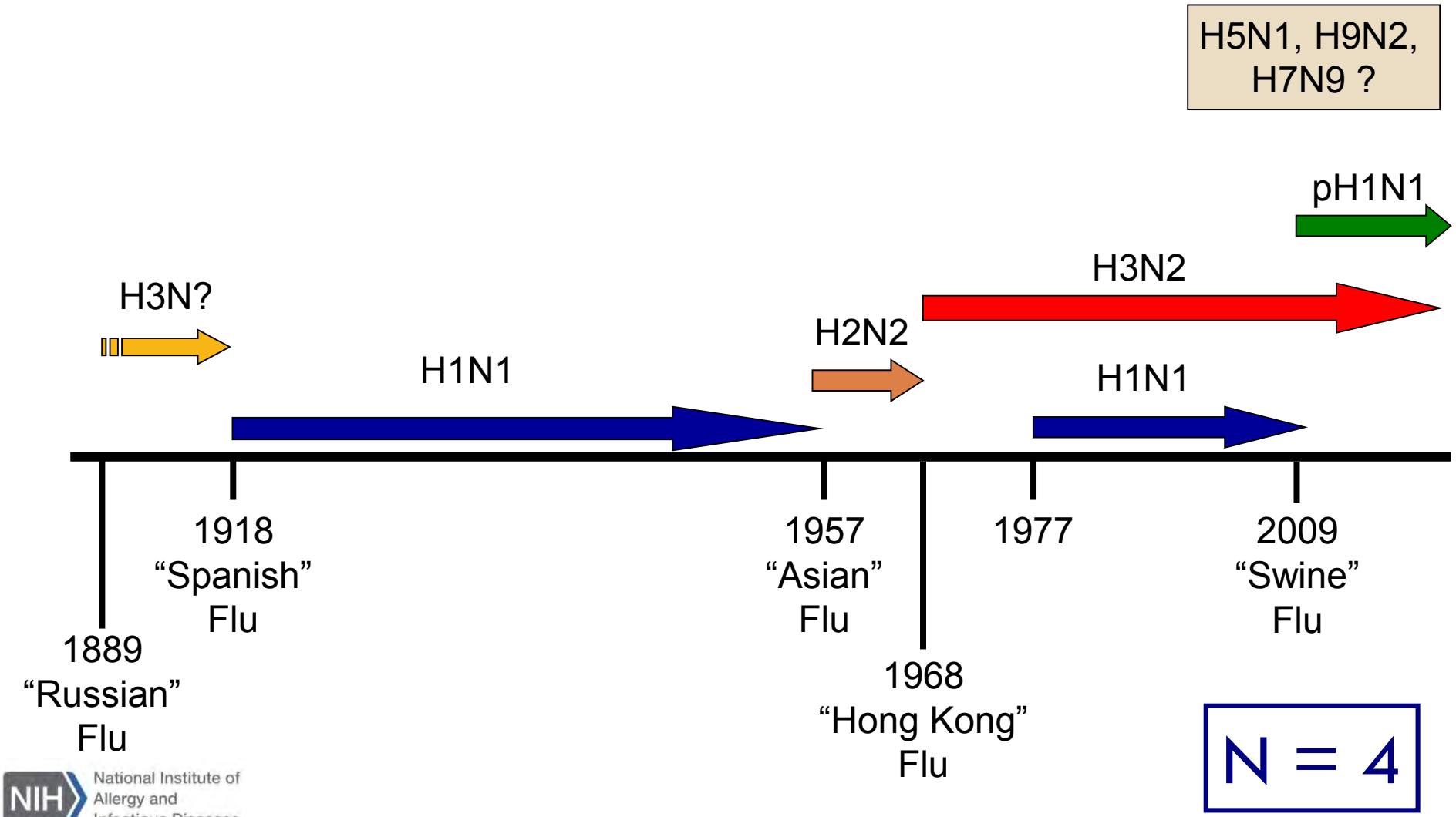
Dugan, et al. (2008) *PLoS Path*, 4(5):e1000076

Influenza A Virus Host Switch

Human Influenza A Timeline

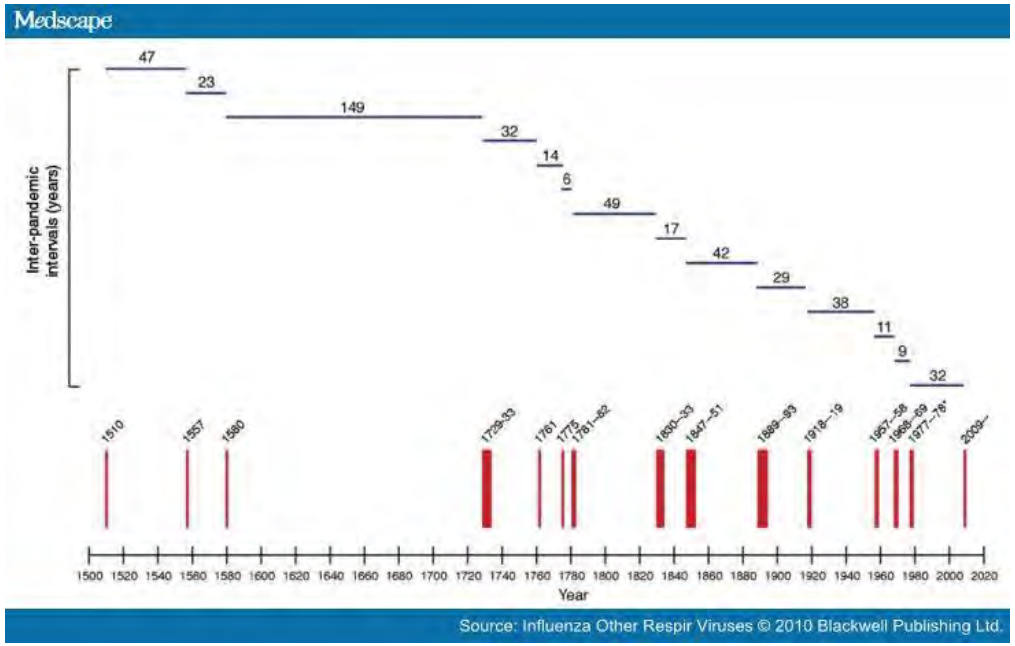


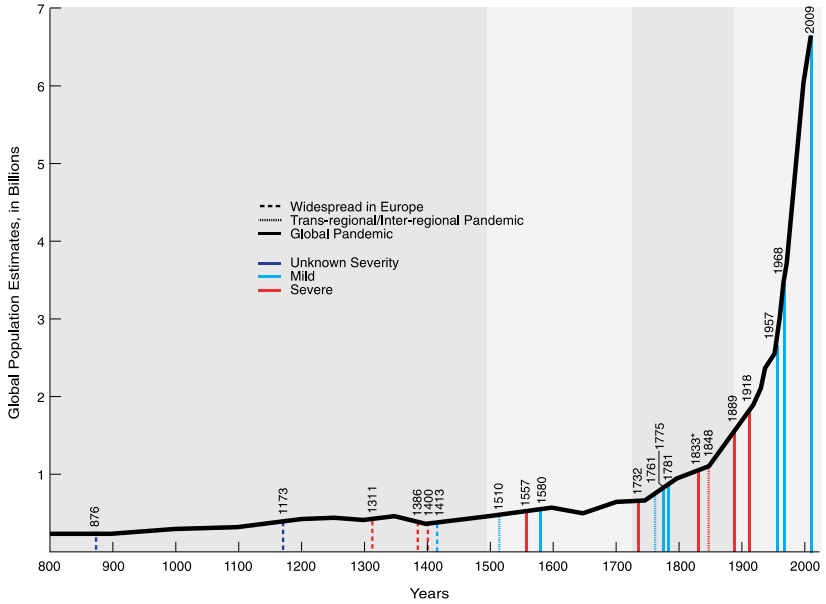
Mortality Impact of Influenza Pandemics

1918 “Spanish” flu (H1N1):	• 675,000 deaths in the U. S.
1957 “Asian” flu (H2N2):	• 70,000 deaths in the U. S.
1968 “Hong Kong” flu (H3N2):	• 30,000 deaths in the U. S.
2009 “Swine” flu (H1N1):	• 12,000 deaths in the U. S.

Influenza Pandemics in History

- ~14 pandemics in last 500 years
- Average interpandemic period ~36 years





Morens & Taubenberger. 2011 Rev Med Virol. 21:262-84

Hunting for the 1918 Influenza Virus

- Concept of viruses as infectious agents still new in 1918
- No isolates of virus made during pandemic
- Influenza A viruses first isolated from pigs in 1930 and from humans in 1933

1918 Influenza Autopsy Cases

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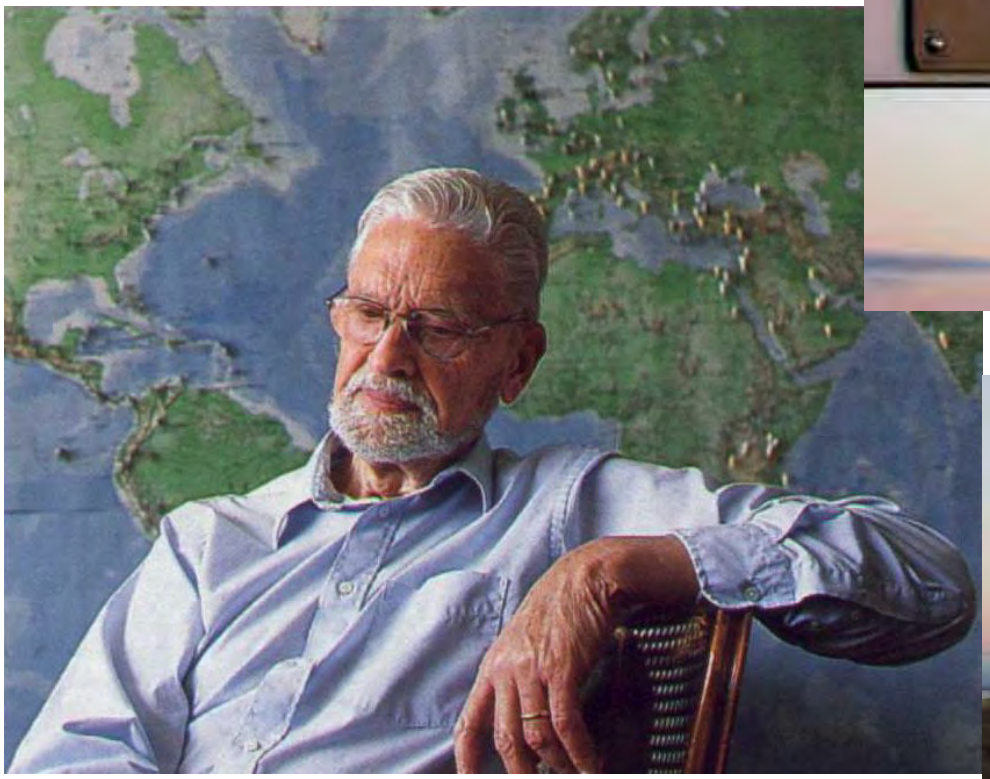
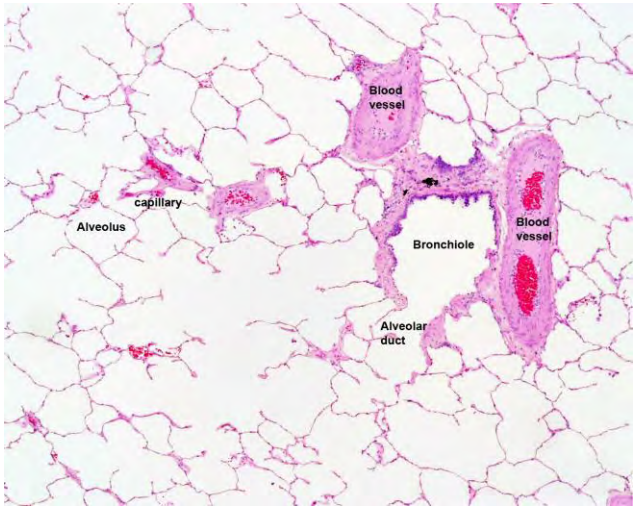
Taubenberger, *et al*. 1997 *Science.* 275:1793
Taubenberger, *et al*. 2005 *Nature*. 437:889

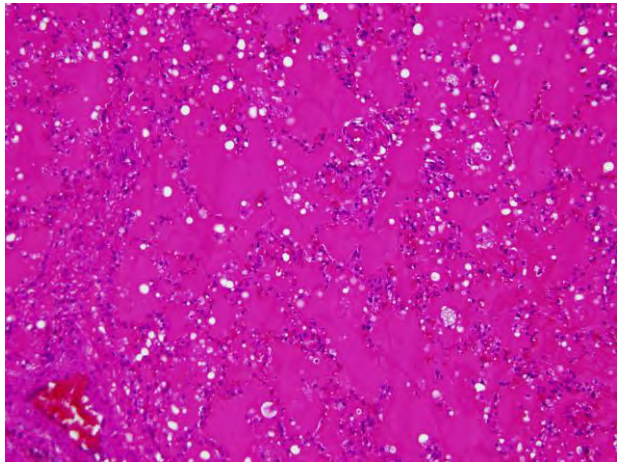
Johan Hultin, M.D.

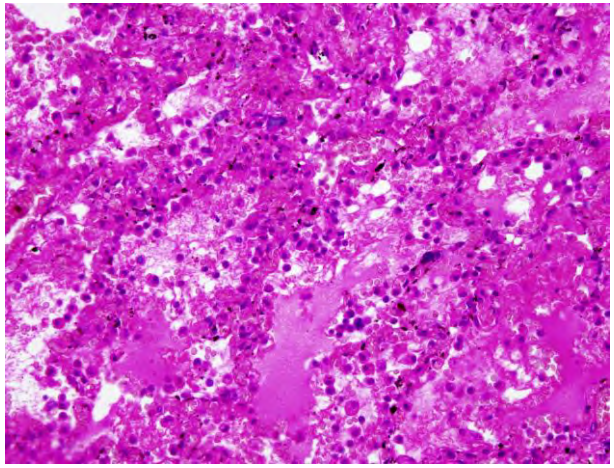


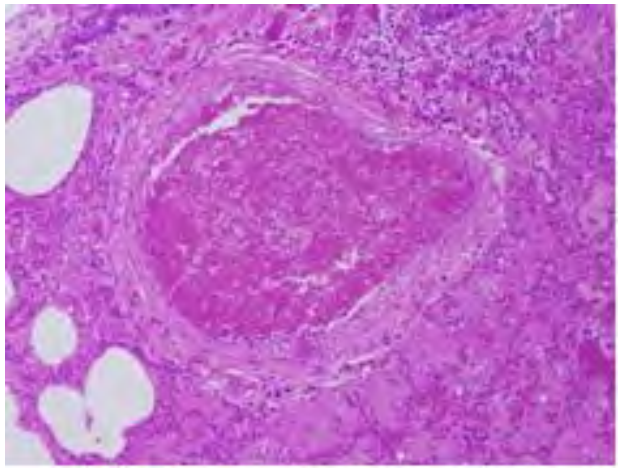
1918 Lung Pathology

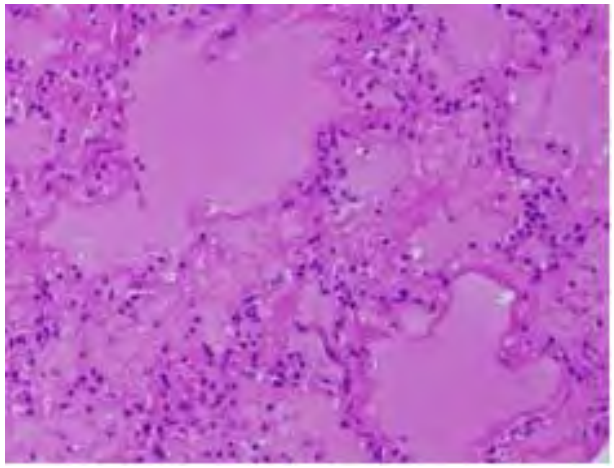
Primary Viral Pneumonia: DAD with edema, alveolitis, thrombi











Taubenberger & Morens 2008 *Ann Rev Path* 3:499
Morens, Taubenberger & Fauci 2008 *JID* 198:962
Kuiken & Taubenberger 2008 *Vaccine* 26(S4):D59

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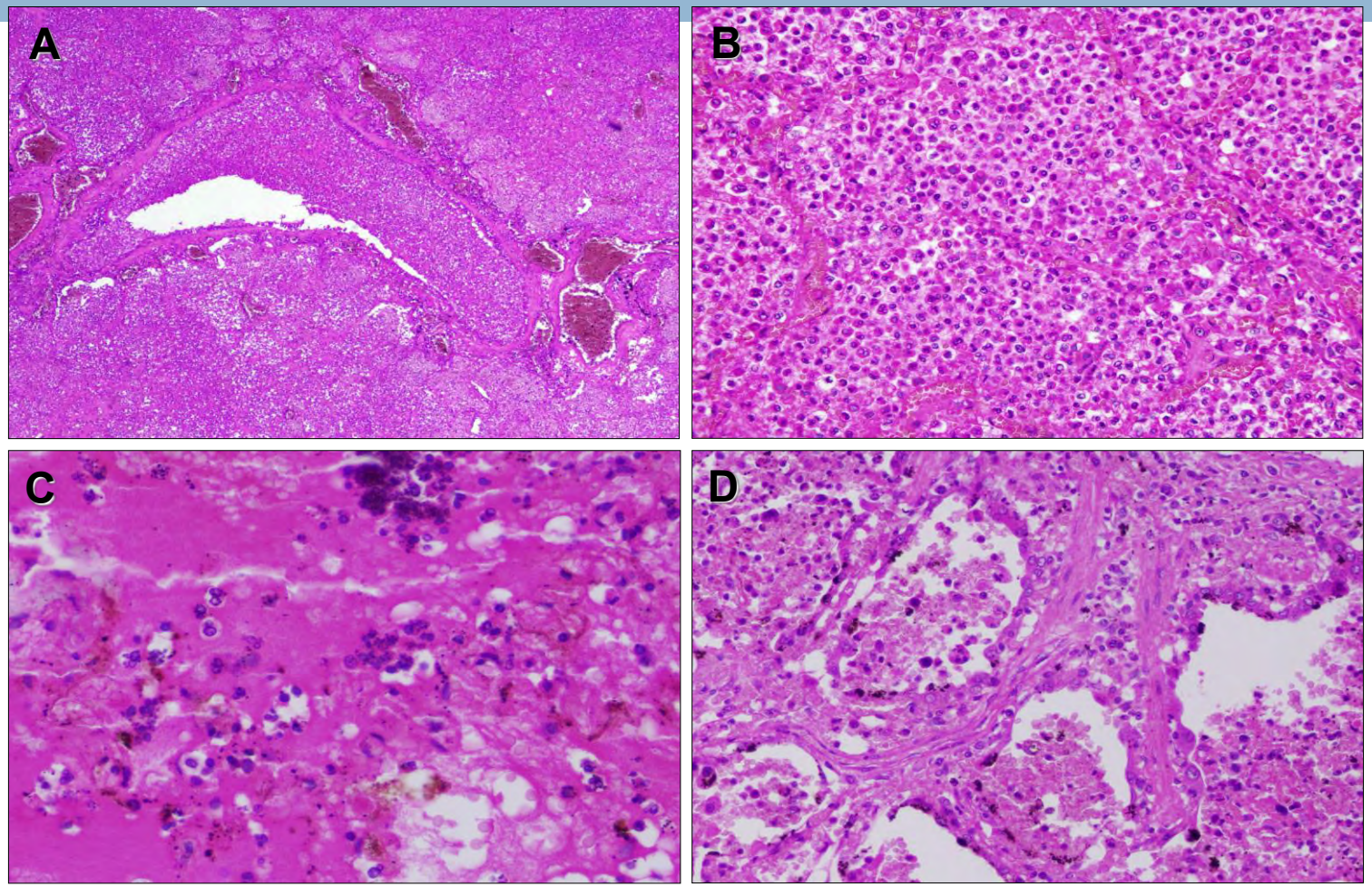
1918 Lung Pathology

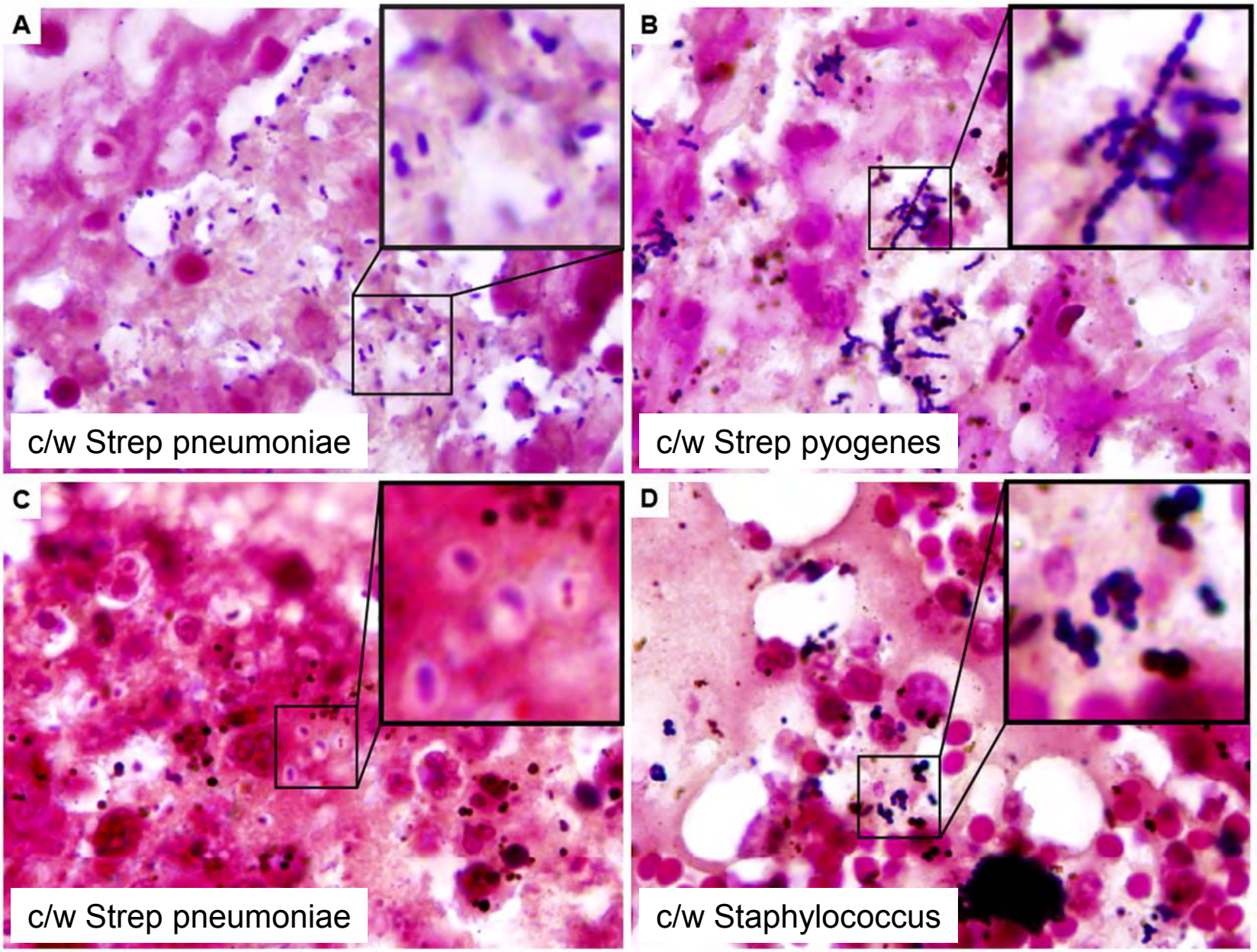
Secondary Bacterial Pneumonia and Repair



Taubenberger & Morens 2008 *Ann Rev Path* 3:499
Morens, Taubenberger & Fauci 2008 *JID* 198:962
Kuiken & Taubenberger 2008 *Vaccine* 26(S4):D59

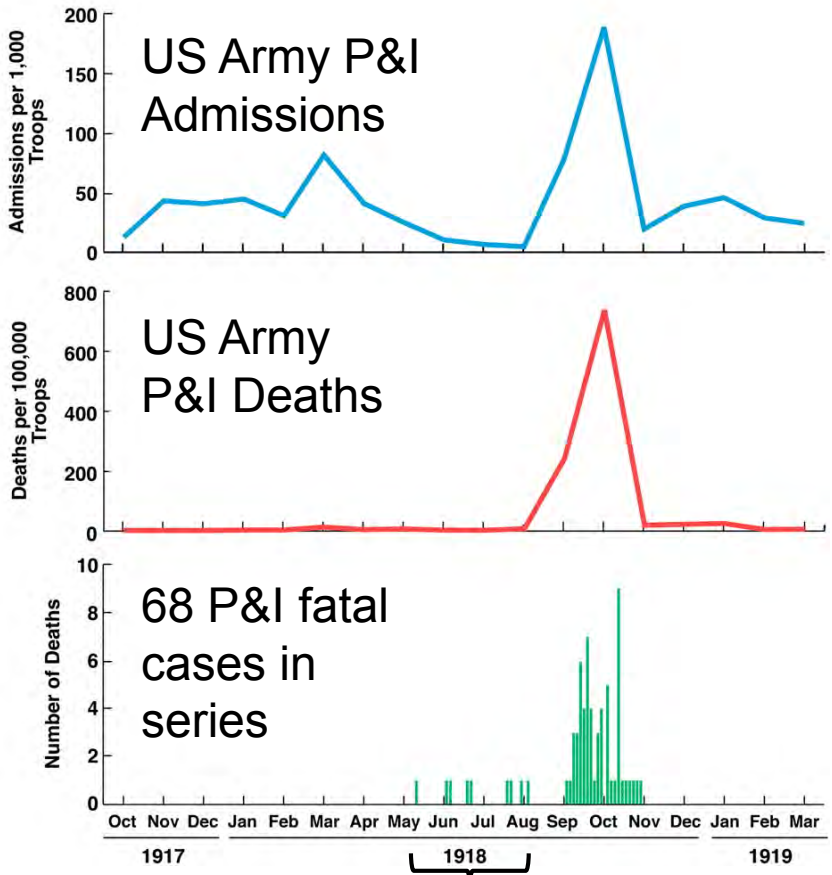
1918 H1N1 Autopsy Study

National Institute of Allergy and Infectious Diseases



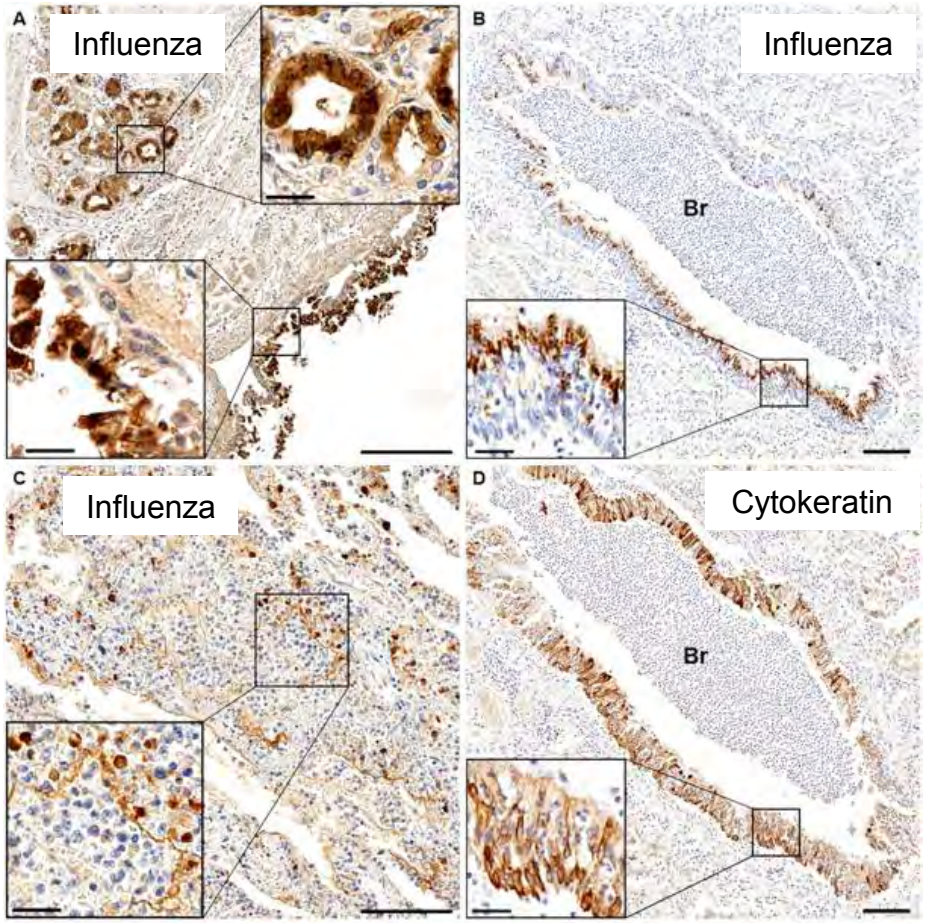
1918 H1N1 Autopsy Study

Analysis of 68 fatal 1918 pneumonia cases

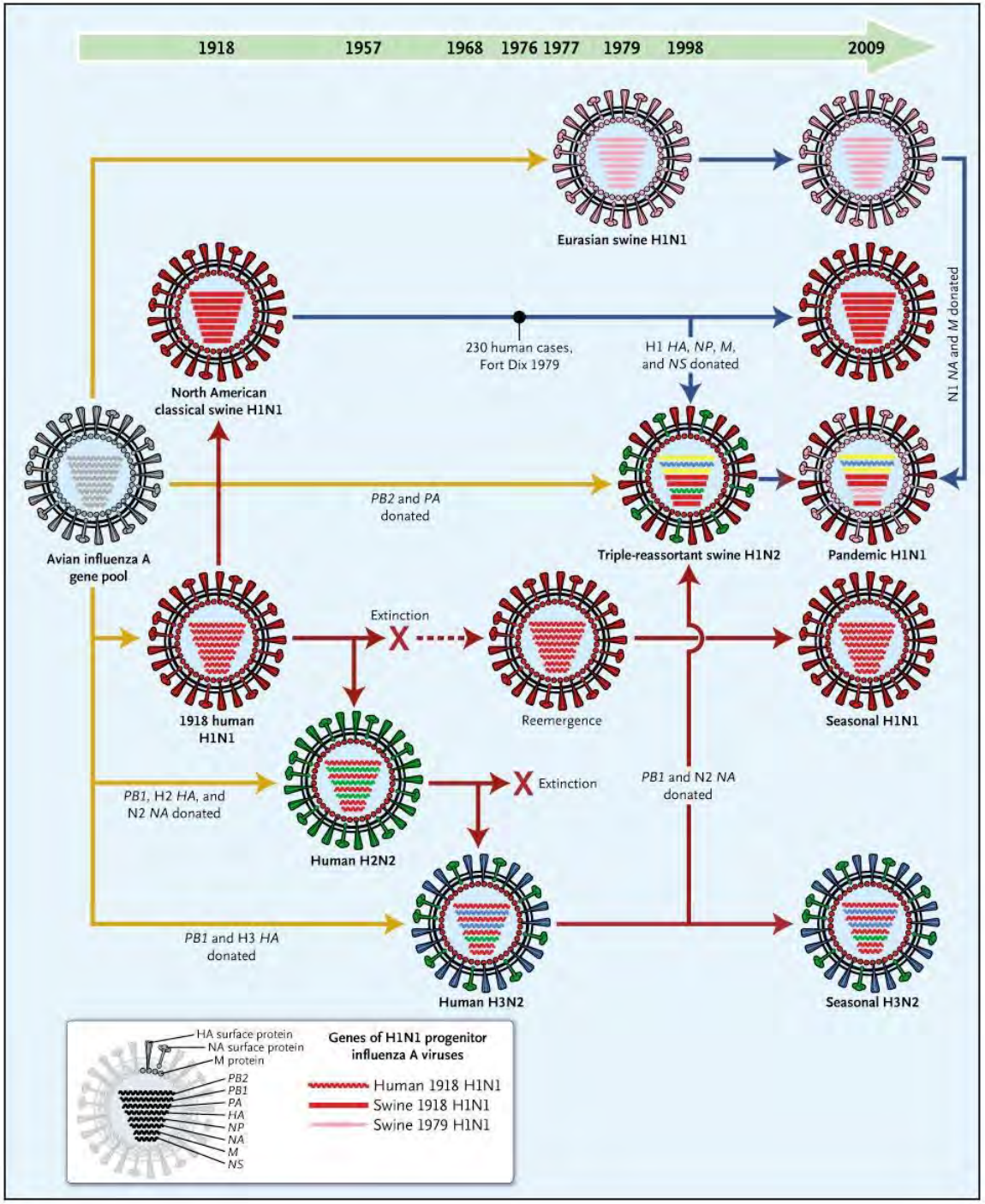


9 spring-summer cases

Viral Antigen Distribution



Sheng *et al.* 2011 *PNAS* 108:16416



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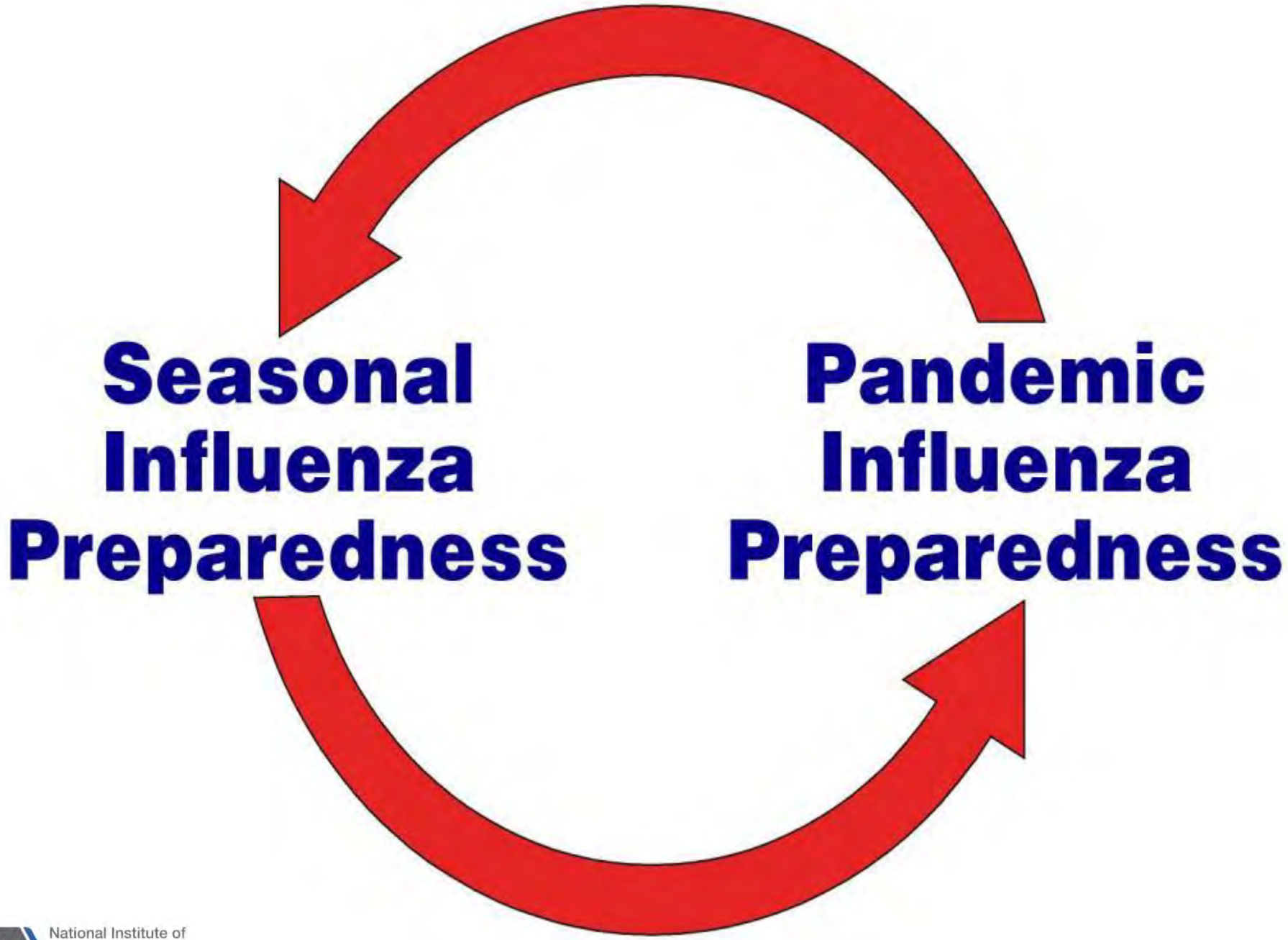
- Since 1918 all pandemic and seasonal influenza viruses descended from the 1918 virus

- All influenza mortality in last 100 years ultimately due to one viral introduction

- Concept of ‘pandemic era’

Morens, *et al*. 2009 *NEJM*. 361:225-229



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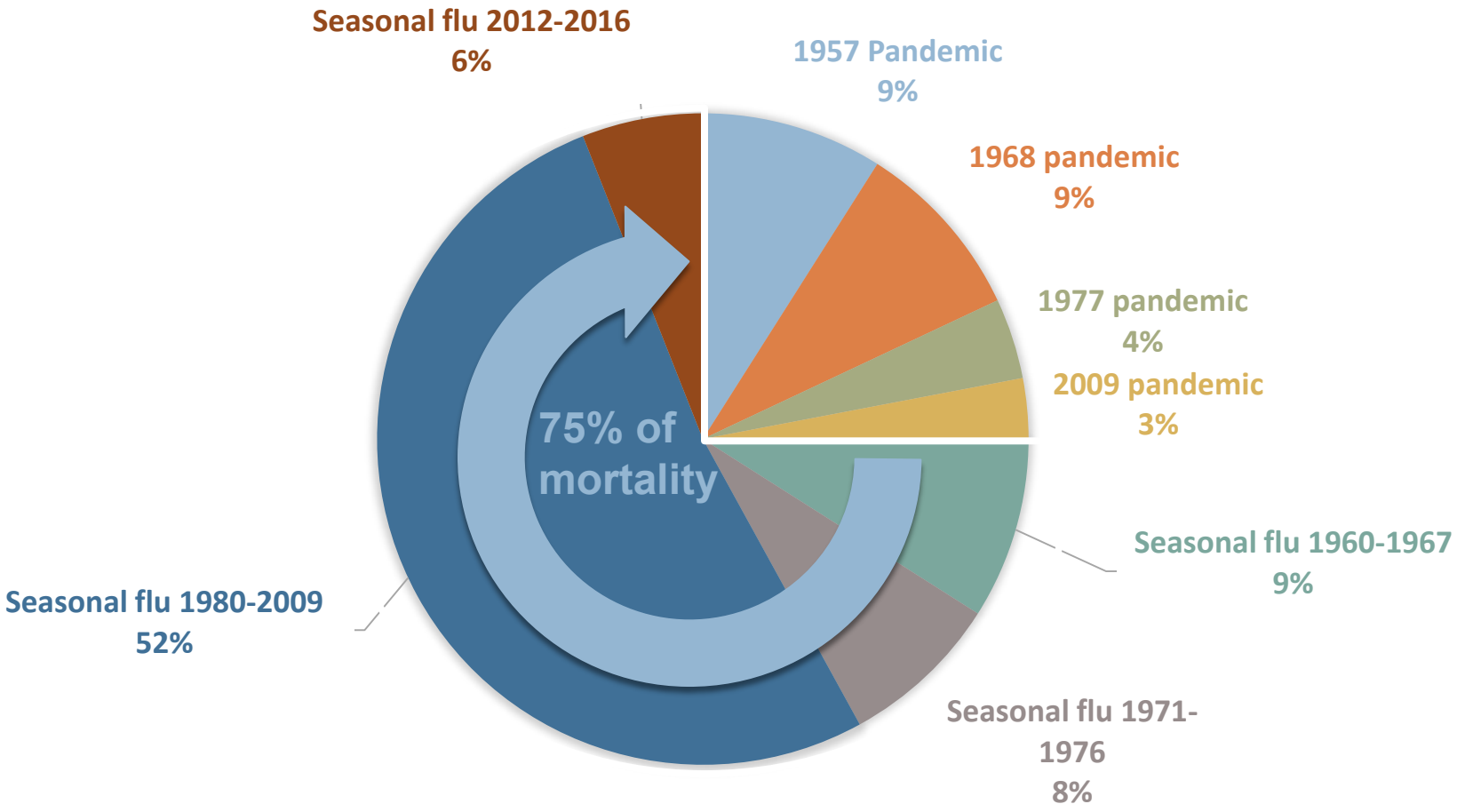
Seasonal Vs. Pandemic Influenza Mortality



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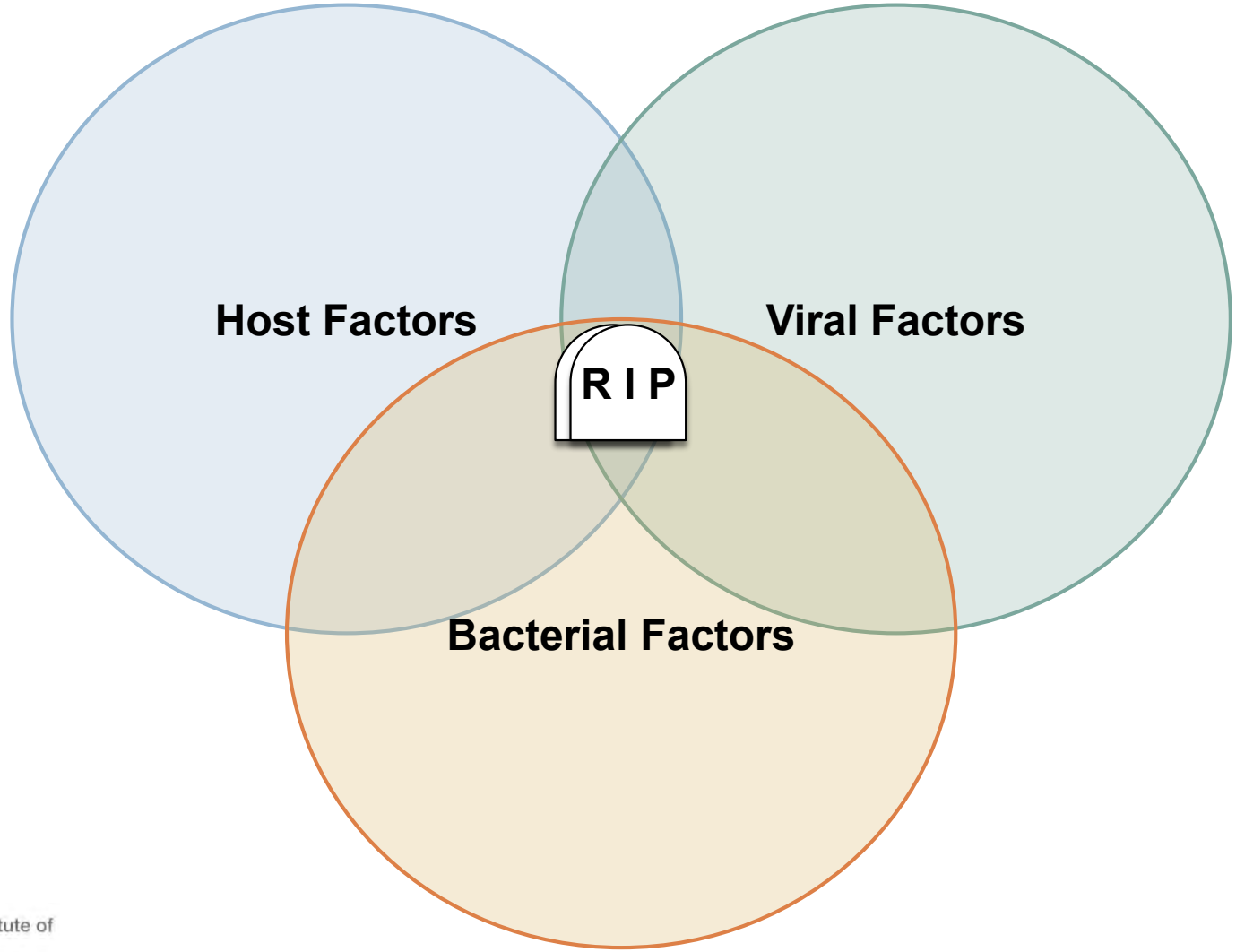
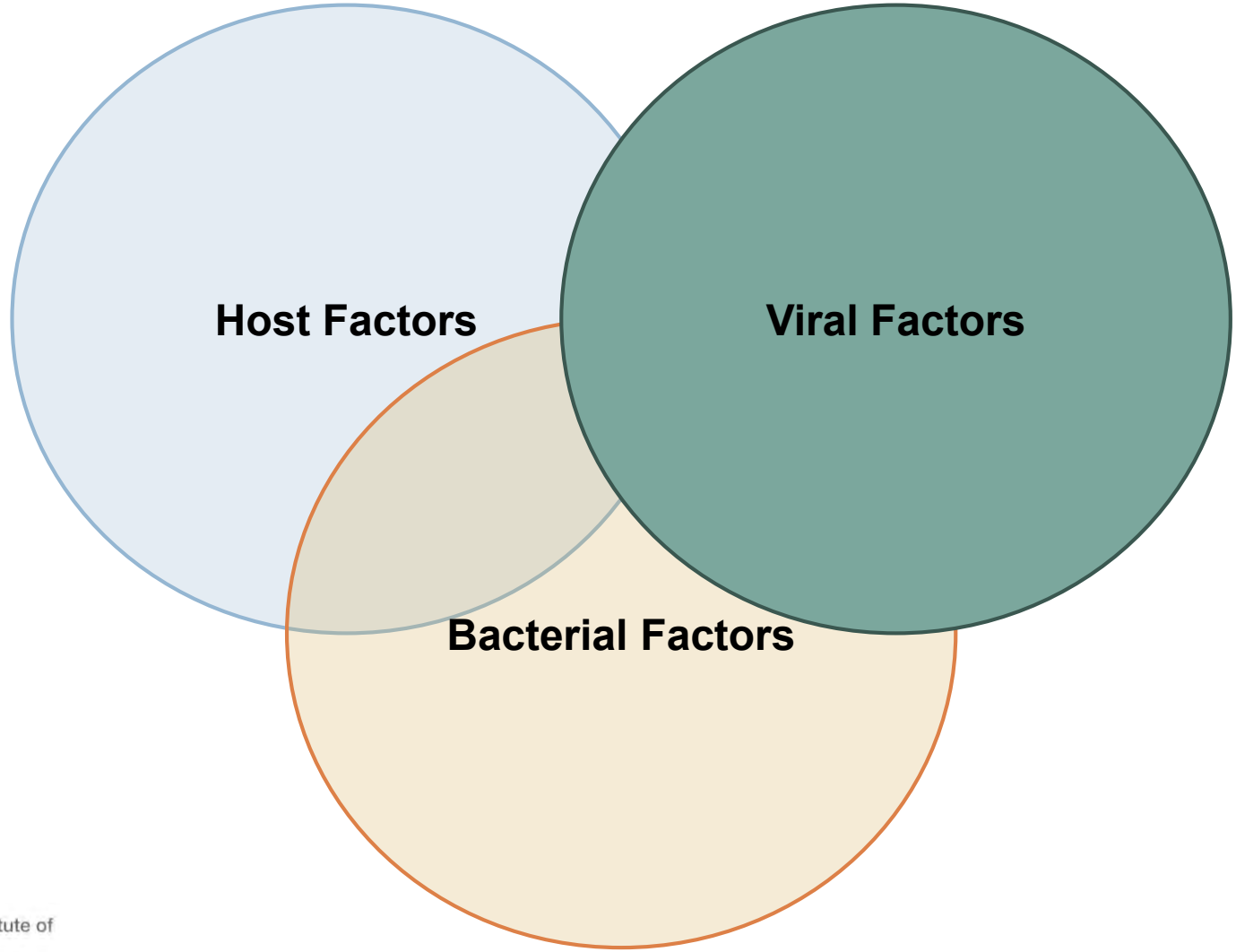
Lessons Learned

- Pandemics are unpredictable in their origin, timing, and severity
- The age-specific “W” mortality pattern of the 1918 pandemic remains unelucidated
- The 1918 pandemic epidemic ‘waves’ were not uniform in character or timing
- Concept of ‘pandemic eras’
- Almost all human cases of influenza in last 100 years ultimately due to a single founder virus in 1918
- In general, most influenza mortality collectively occurs in seasonal influenza not in pandemic influenza years

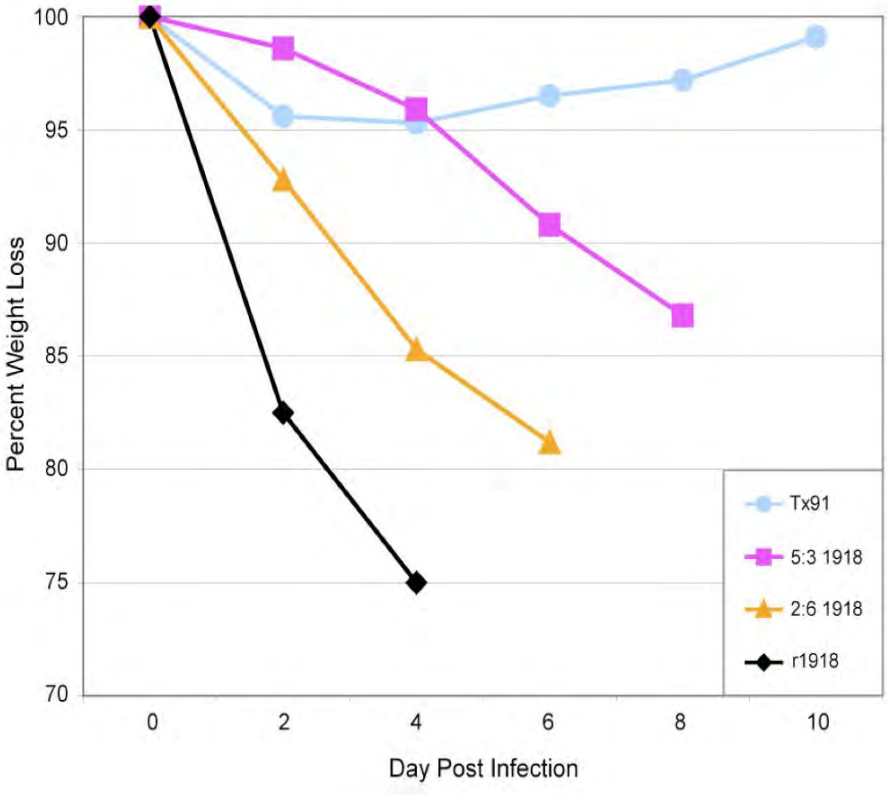
Influenza Pathogenicity



Influenza Pathogenicity

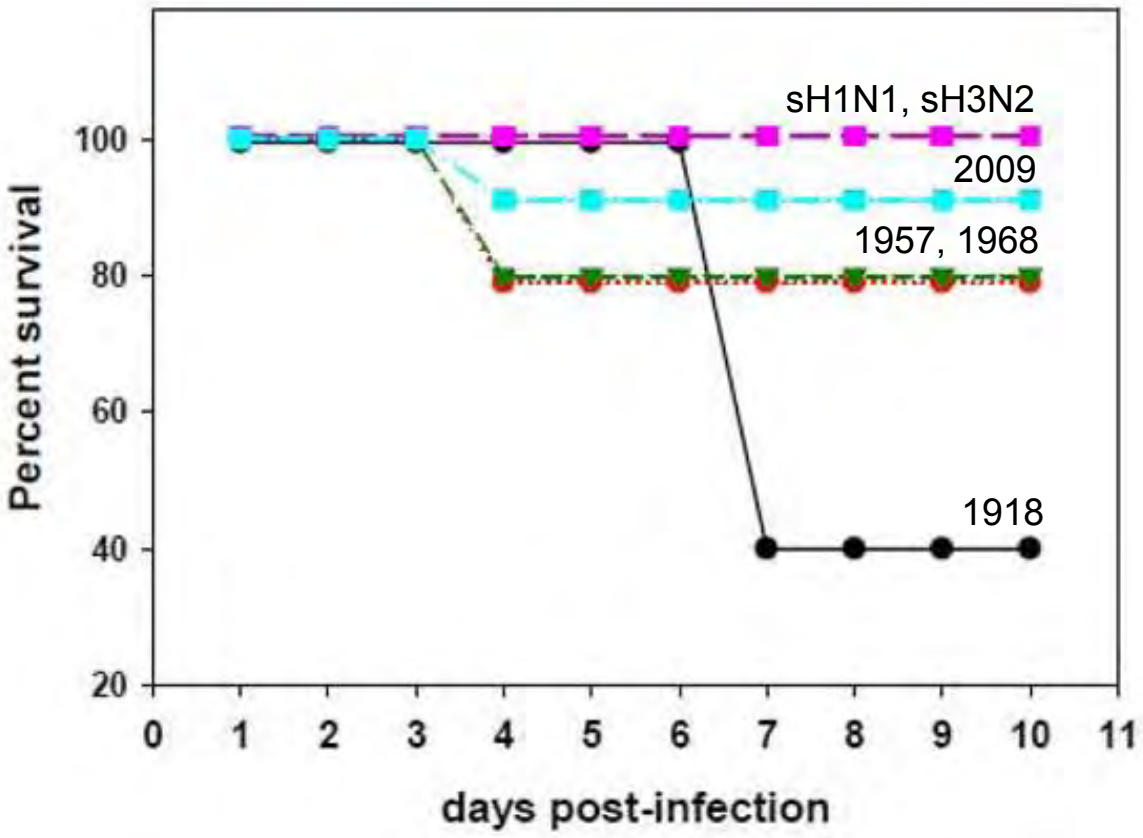


1918 Influenza Pathogenesis



Kash, et al. 2006 *Nature* 443:578

Pandemic HA Virulence Factors



- Isogenic viruses containing pandemic HA's cause severe disease
- 1918 > 1957,1968, or 2009
- Seasonal H1 or H3 bearing viruses did not cause severe disease

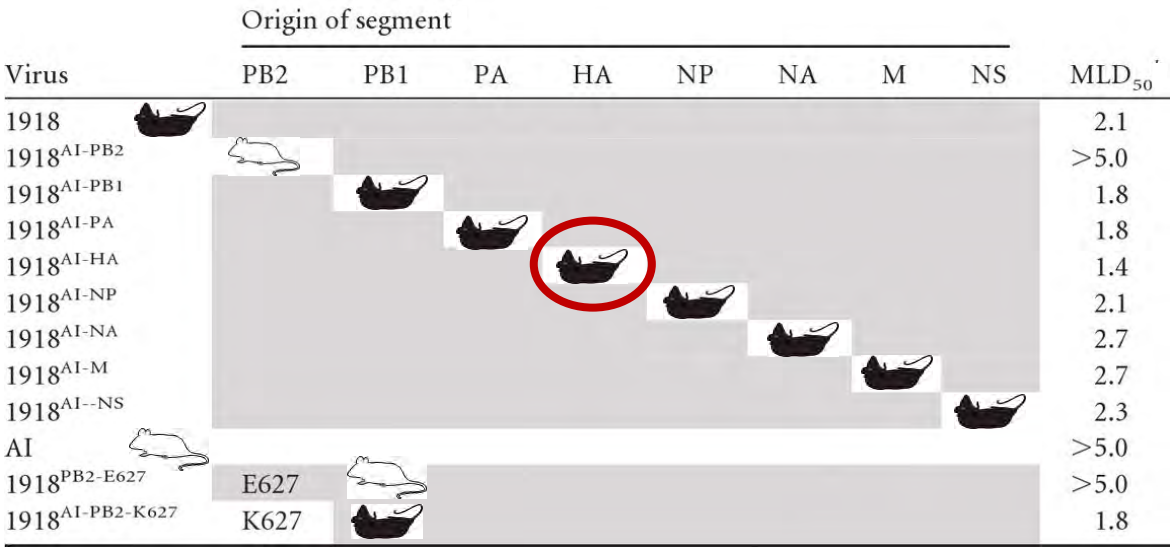
Qi, *et al*. 2011 *Virology* 412:426-34

Mapping Virulence of the 1918 Influenza Virus - 1918-Avian Single Gene Reassortants

- 1918 HA is the main virulence factor in pathogenicity in mice, ferrets, NHP
- 1918 virus has a very avian-like genome
- Avian H1 HAs did not attenuate 1918 virus, and share virulence with 1918
- 1918 virus virulence therefore likely not pandemic virus-specific but inherited from a low path avian H1 ancestor

1918 gene

LPAI gene

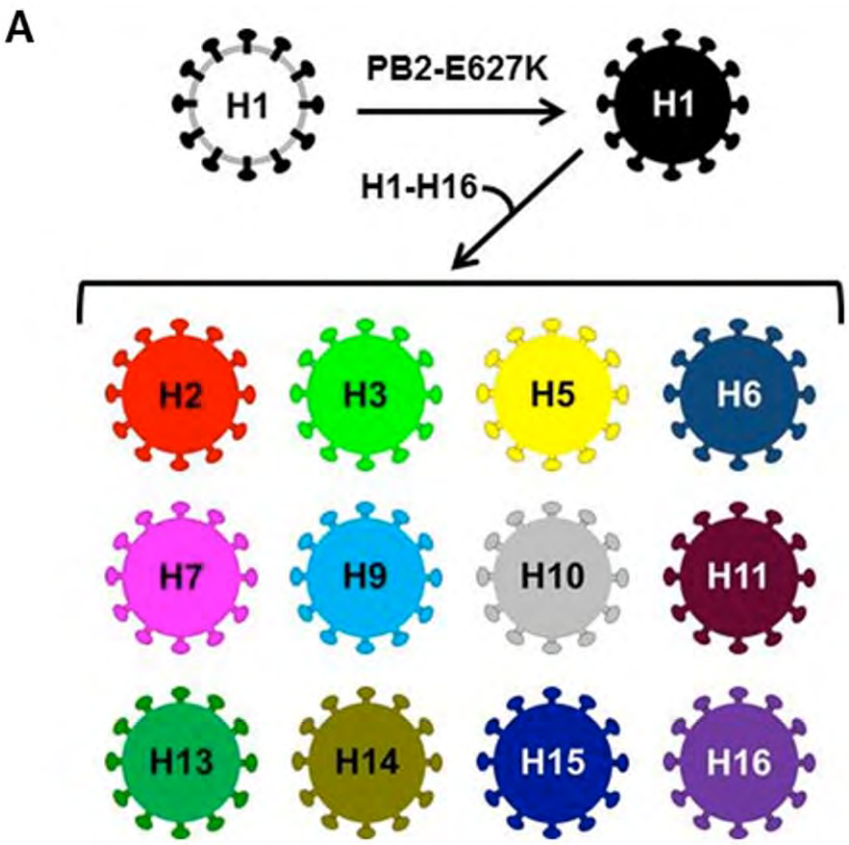


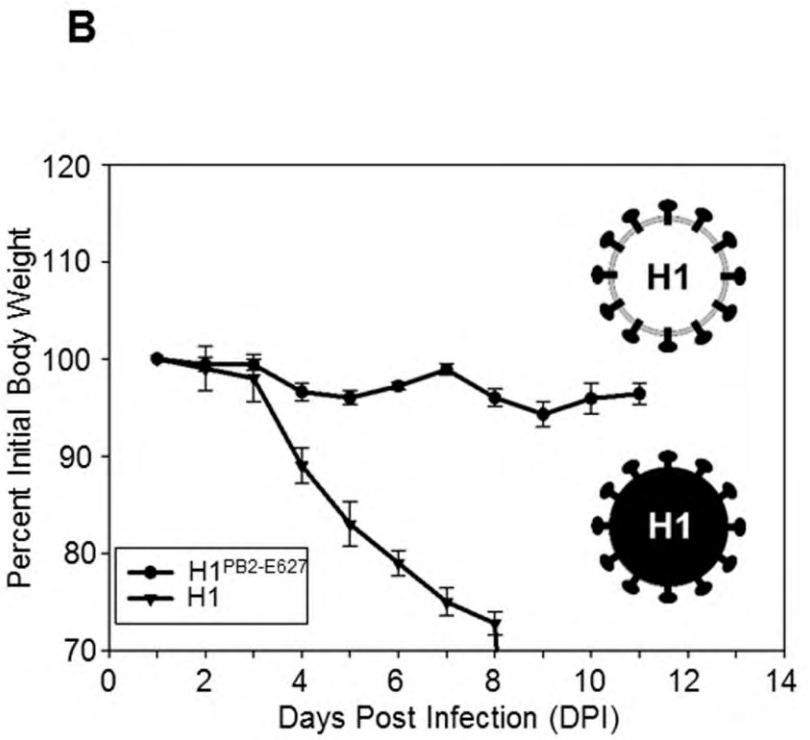
What about other low path avian influenza (LPAI) HA subtypes?

National Institute of Allergy and Infectious Diseases

Qi, *et al*. 2012 *J Virol* 86:921

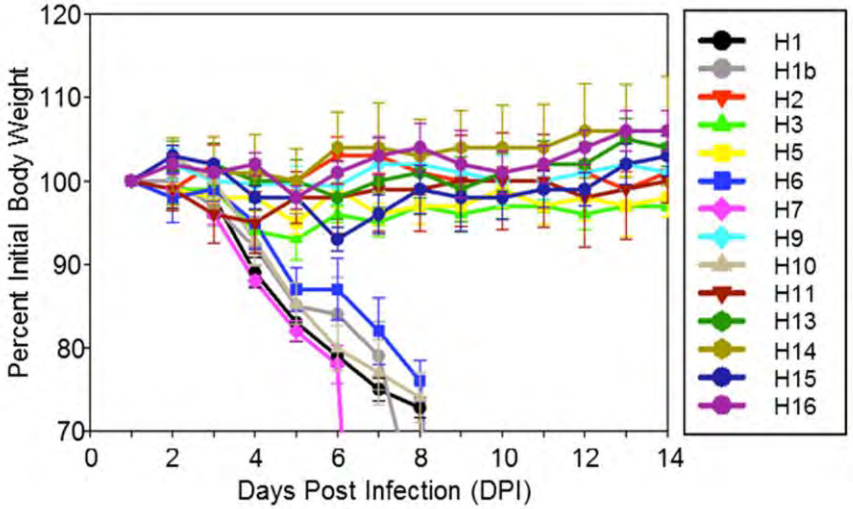
What about other LP Avian HA Subtypes?

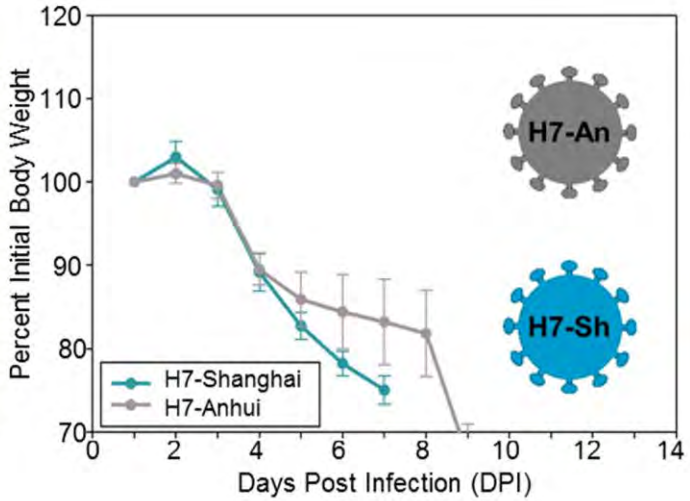




Qi, *et al*. 2014 MBio. 5:e02116-14

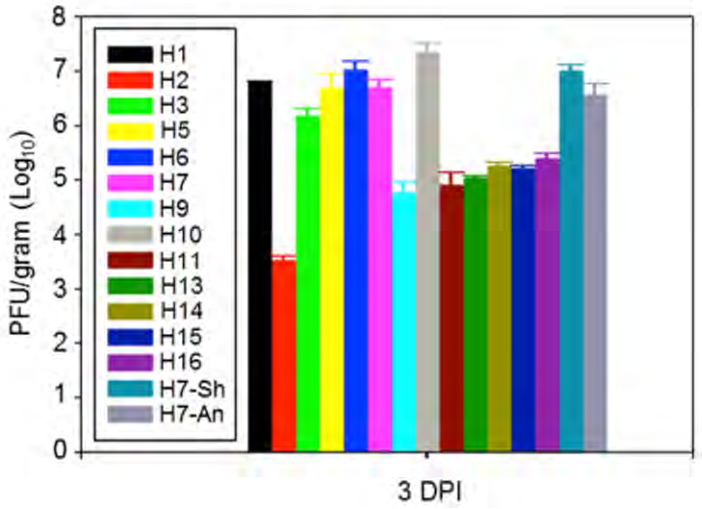
LP Avian Virus Mouse Pathogenicity





<u>Pathogenic viruses:</u>

- H1, H6, H7, H10, H15
- Lung titers did not correlate with pathogenicity

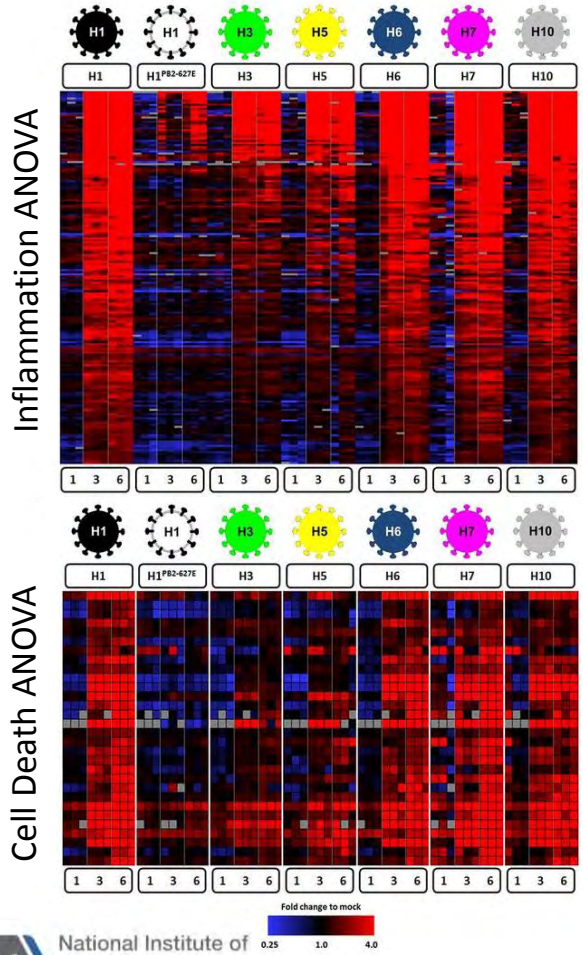


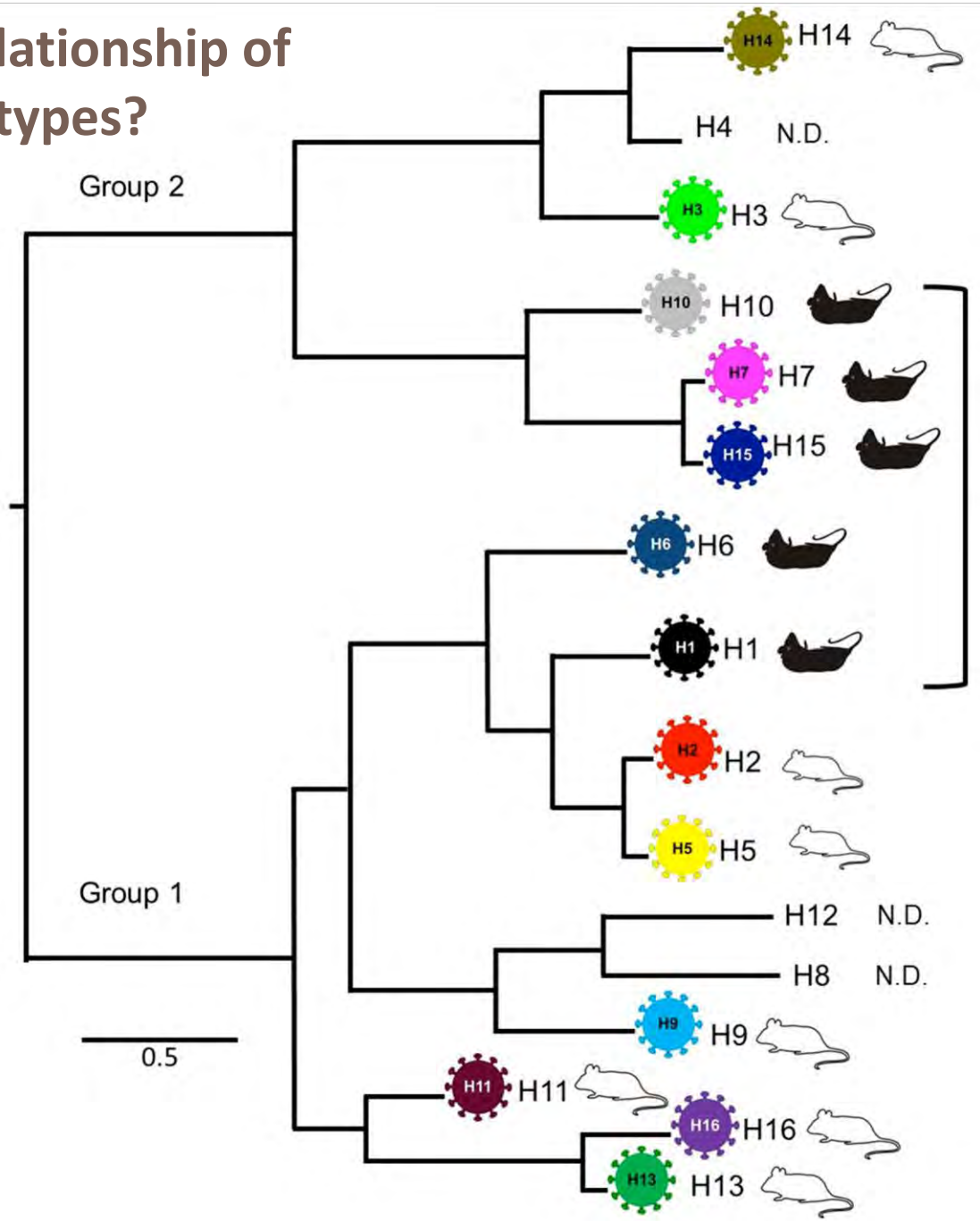
National Institute of Allergy and Infectious Diseases

Qi, *et al*. 2014 MBio. 5:e02116-14

Structural/ Functional Relationship of Pathogenic Avian HA Subtypes?

H1, H6, H7, and H10 inflammatory responses similar to the 1918 virus





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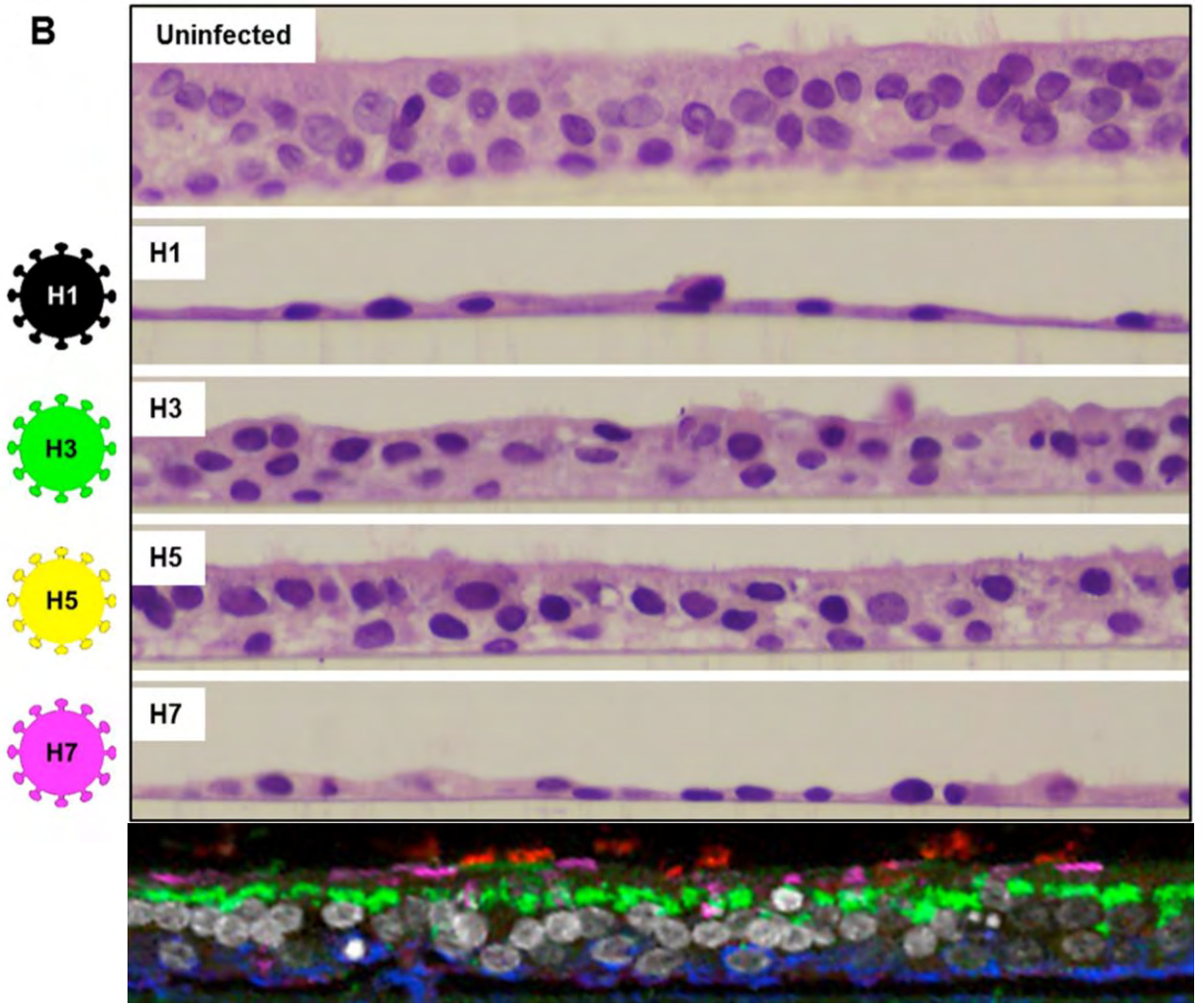
Qi, *et al*. 2014 mBio. 5:e02116-14

NHBE Culture – Cytopathicity Correlates with Mouse Pathogenicity



National Institute of Allergy and Infectious Diseases

Qi, *et al*. 2014 MBio. 5:e02116-14
Davis, et al. 2016 Virol. 493:238-246

China reports first human case of H10N8 avian flu

Filed Under: **Avian Influenza (Bird Flu)**
Jim Wappes | Editorial Director | CIDRAP News | Dec 17, 2013

Share Tweet Email Print & PDF

A 73-year-old woman in Jiangxi province in China has died from an H10N8 avian flu infection, Hong Kong's Centre for Health Protection (CHP) said today, the first report of that strain infecting humans.

The woman, whose immune system was compromised, had an underlying illness and had visited a li
statement
30, was di
died Dec 6

Taiwan reports first human H6N1 infection

Filed Under: **Avian Influenza (Bird Flu)**
Lisa Schnirring | Staff Writer | CIDRAP News | Jun 21, 2013

Share Tweet Email

Health authorities in Taiwan today announced the first known human infection with H6N1 avian influenza, in a 20-year-old woma
pneumonia in May and has sinc

The virus was identified at a tim
officials were on heightened aler
The woman's novel flu infection
attention of Taiwanese health of
after the region had identified its
man who had recently traveled t
area for work.

H7N9 hospitalizes 6 more in China

Filed Under: **Avian Influenza (Bird Flu)**; **H7N9 Avian Influenza**
Lisa Schnirring | Staff Writer | CIDRAP News | Jan 17, 2014

Share Tweet Email Print & PDF

Six H7N9 influenza infections were reported in two Chinese provinces and the city of Shanghai today, keeping the volume of new cases within striking distance of peak activity the country saw during the outbreak's first wave last spring.

China's National Health and Family Planning Commission today addressed the quickly rising number of H7N9 cases, especially since the first of the year, according a report today from Xinhua, the state news agency. It said 28 cases have been reported so far.

Luke Seall / iStockphoto

Recent AIVs causing severe zoonotic infections have included HA subtypes H6, H7, H10

Zoonotic Avian Influenza Infections and the Risk of a Future Pandemic

- H5N1: 860 documented cases, 454 deaths
  - Reported CFR 53%
  - WHO, 2003-2017, as of December 2017
- H7N9: 1623 confirmed with 620 deaths
  - Reported CFR 38%
  - WHO, 2013-2017, as of December 23, 2017
- Problems associated with current vaccine strategies:
  - Zoonotic viruses continue to evolve, requiring updating stockpiled pre-pandemic vaccine stocks
  - Epizootic outbreaks often do not result in pandemics, and emergence of pandemic viruses cannot yet be predicted

H7N9 avian influenza cases

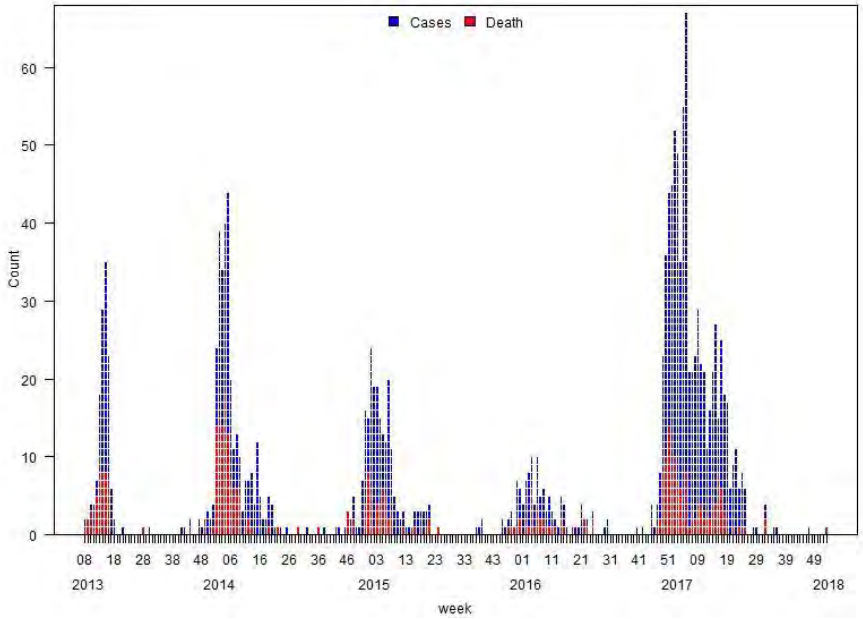
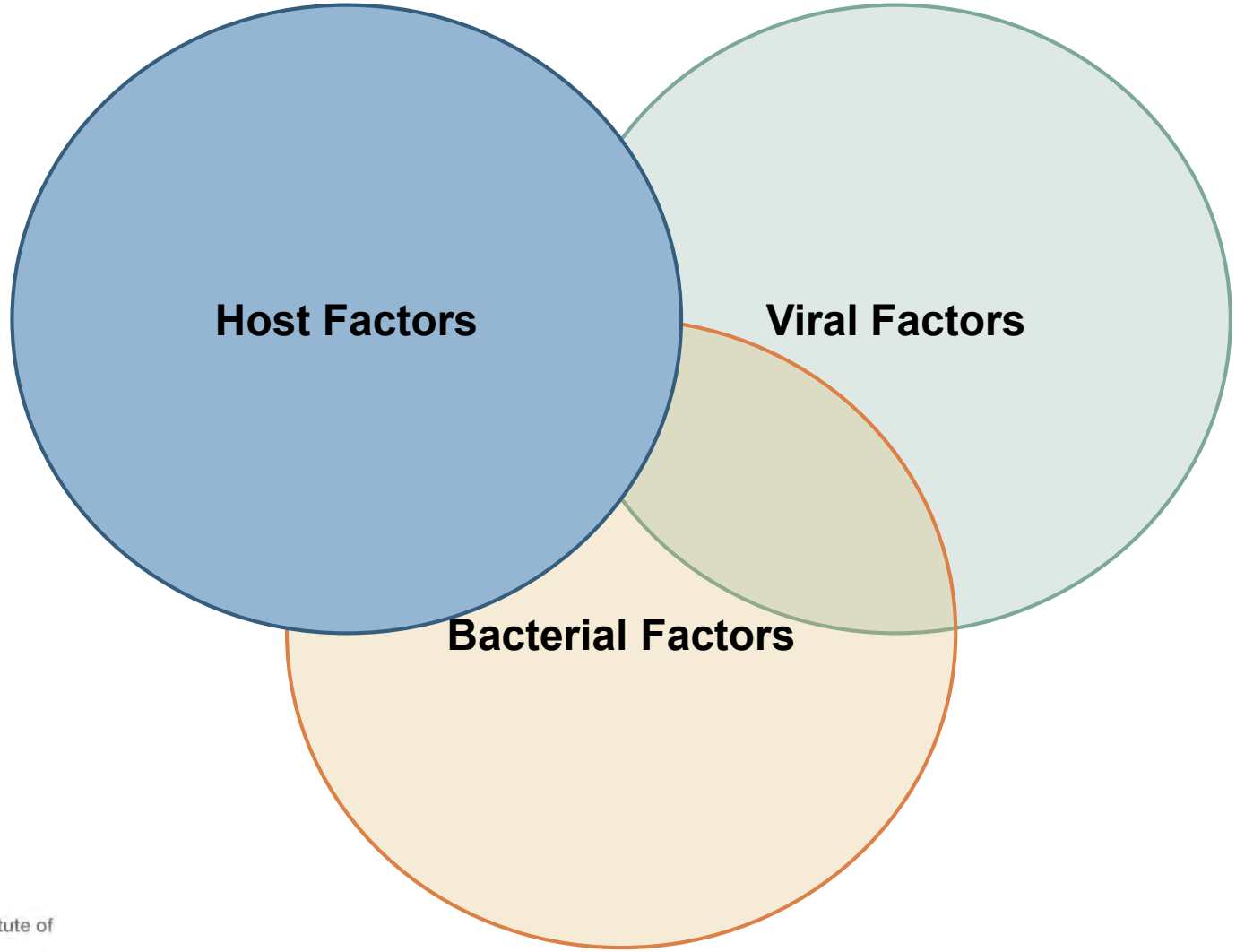


Table 3. Selected Amino Acid Substitutions Observed in H7N9 Case Samples

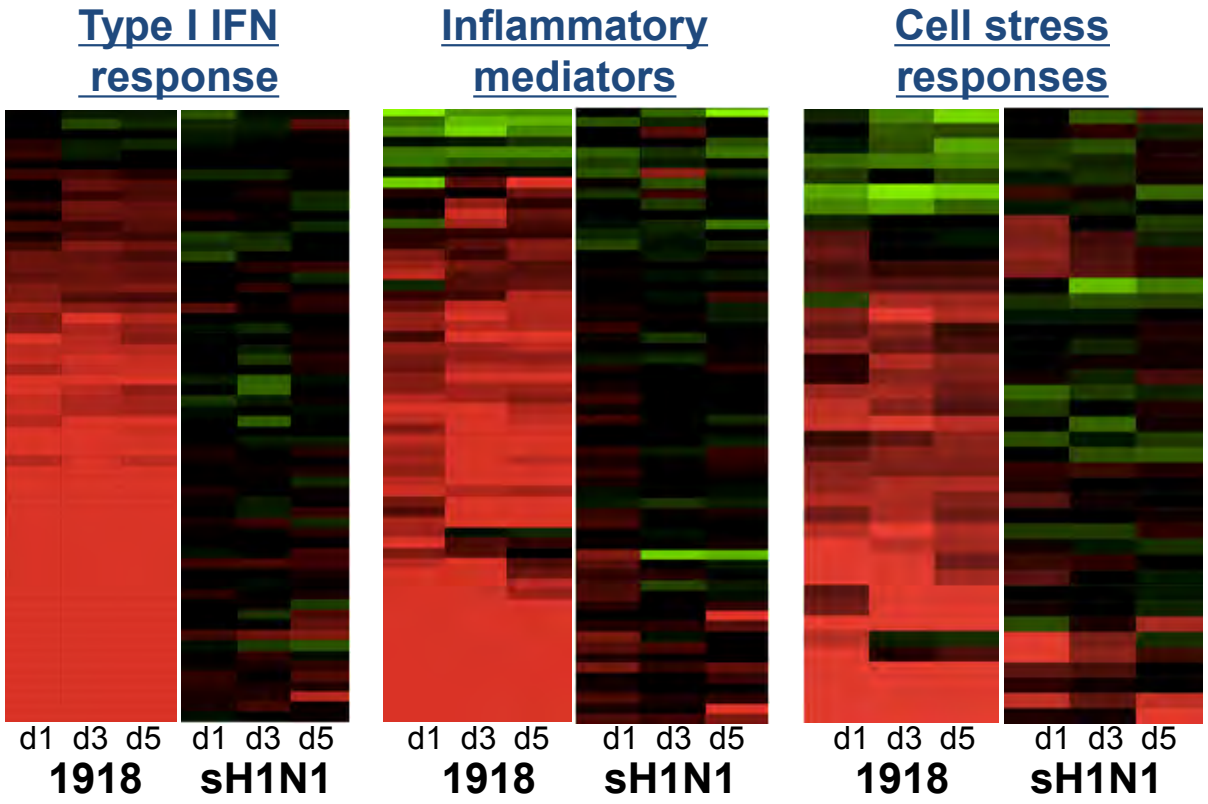
H7N9 Protein[1]	Codon Substitution[2]	Avian H7N9 Consensus[3]	Human H7N9 Consensus[3]	Function/Region[3]	Case Number
HA	V104I	V	V	HA head	14, 16
	S136N	S	S	HA head	17
	A143V	A	A	HA head	17
	R148K	R	R	HA head	17
	L186I	L	L	HA receptor binding	17
	Q235L	Q	L	HA receptor binding	1, 2, 4, 5, 13, 15, 16, 17
	R270K	R	R	HA head	15, 16
	L394I	L	L	HA stalk	8, 10, 12, 13, 14, 15 ,16
	E396A	E	E	HA stalk	12, 17, 19, 20
	S499R	S	S	HA stalk	11, 12, 17, 19, 20
	N551S	N	N	HA cytoplasmic tail	1, 2, 3, 6, 8, 13, 14, 15, 16, 20
	G552R	G	G	HA cytoplasmic tail	1, 2, 3, 6, 8, 13, 14, 15, 16, 20

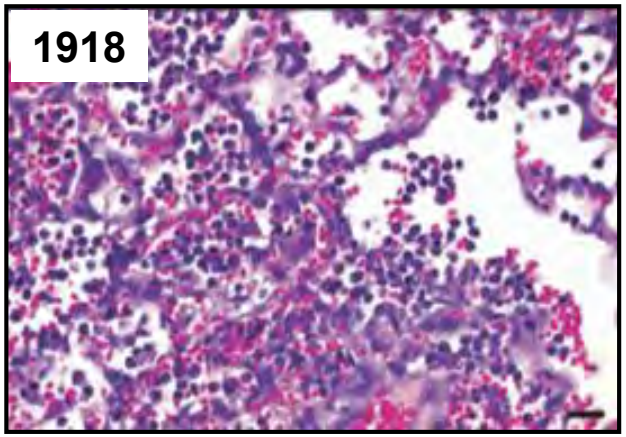
Xiao, et al. 2018 3:e00462-18

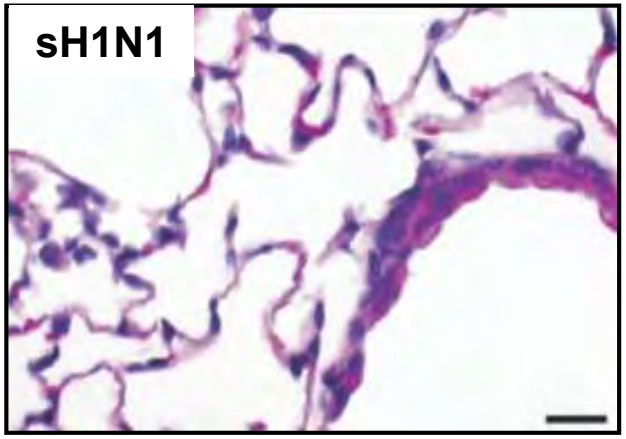
Influenza Pathogenicity



Upregulated Inflammatory Responses During 1918 Infection



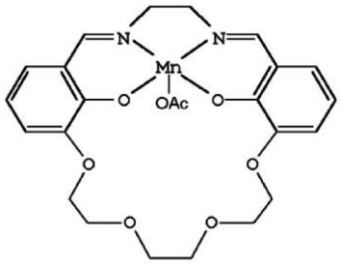




National Institute of Allergy and Infectious Diseases

Kash, et al. 2006 *Nature* 443:578

Treatment with a Catalytic ROS Scavenger Decreases Lung Damage and Increases Survival



EUK-207: organometallic SOD/catalase mimetic

1918 Pandemic Influenza Virus

Daily from day +3 to day +10

EUK-207

Vehicle

4x LD_{50}

H&E

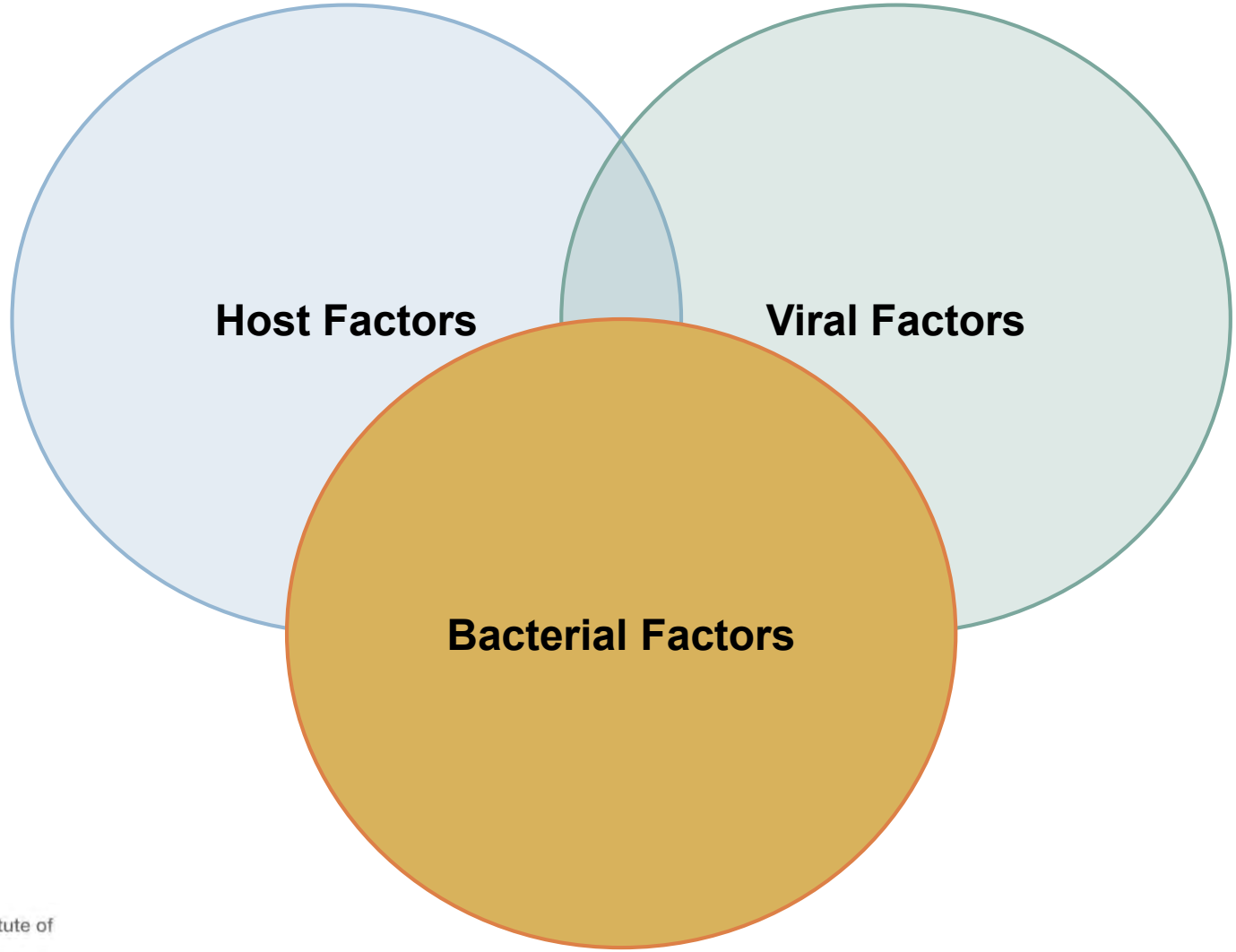
Anti-8-oxo-2'-deoxyguanosine

Pathology

ROS damage

Kash *et al.* 2014 *FRBM* 67:235-47

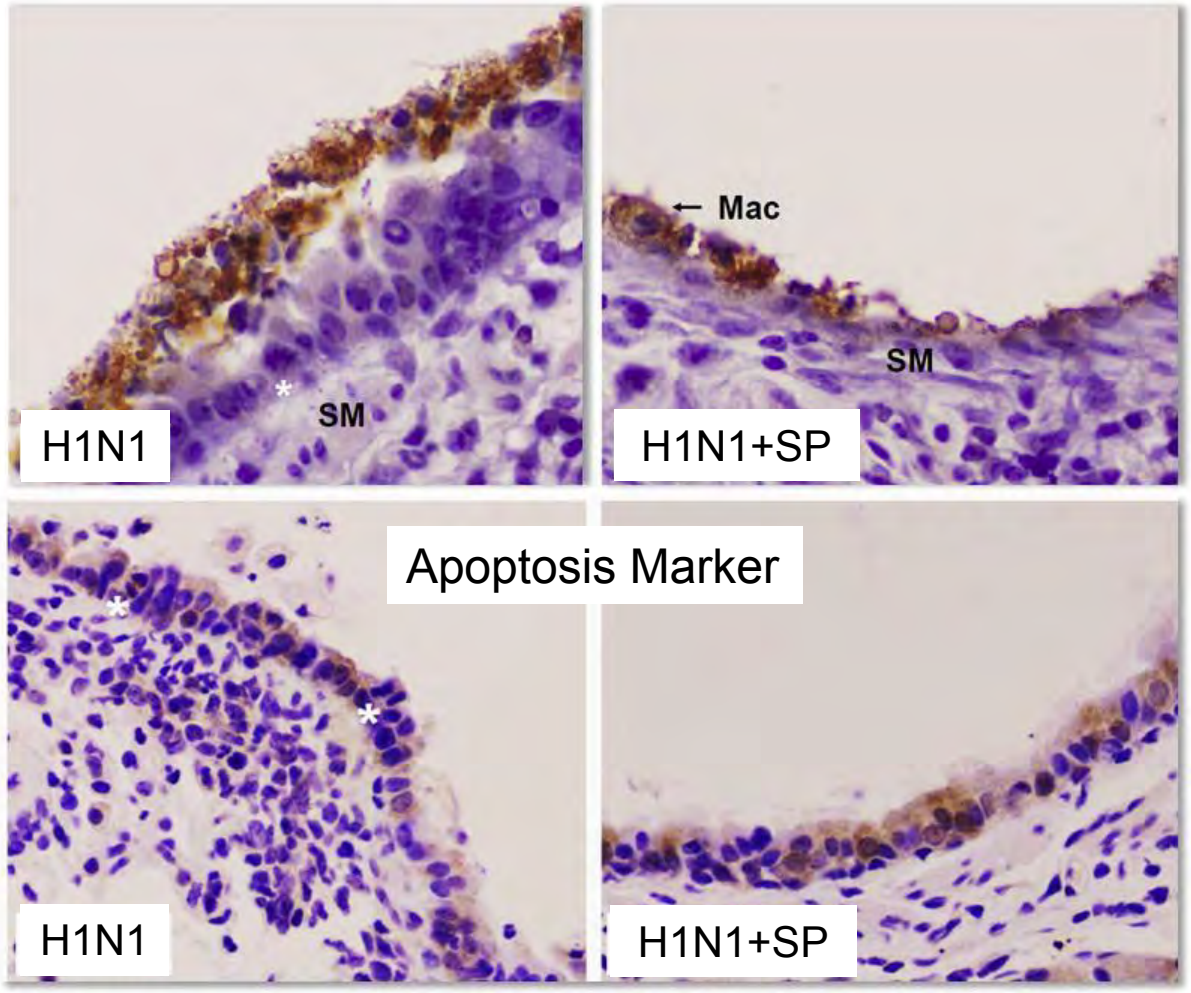
Influenza Pathogenicity



Viral/Bacterial Coinfection is Associated with Loss of Airway Basal Epithelial Cells

IHC for viral antigen

IHC for cCASP3



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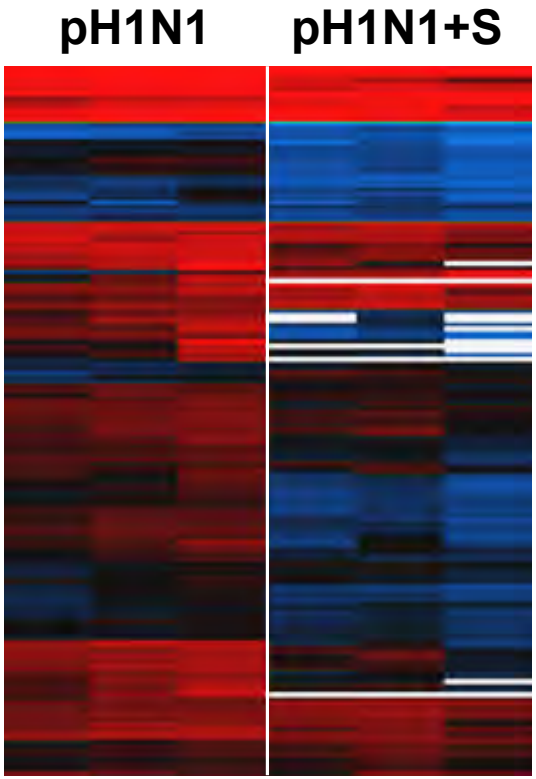
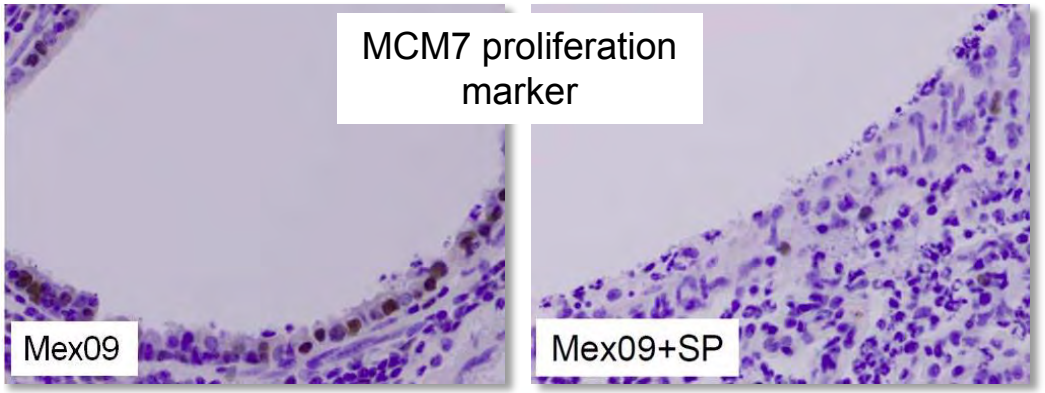
Kash *et al*. 2011 *mBio* 2:e00172

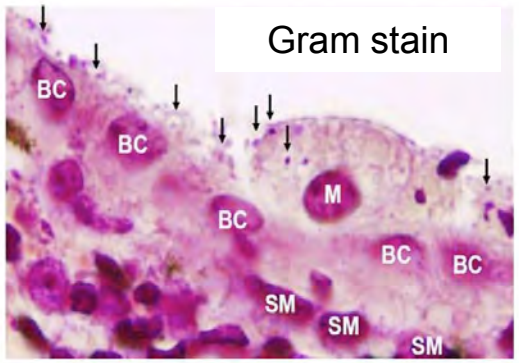
Viral & Bacterial Copathogenesis

pH1N1+SP infection associated with loss of basal cells and absence of re-proliferation and repair of airway epithelial cells



Repair/proliferation genes



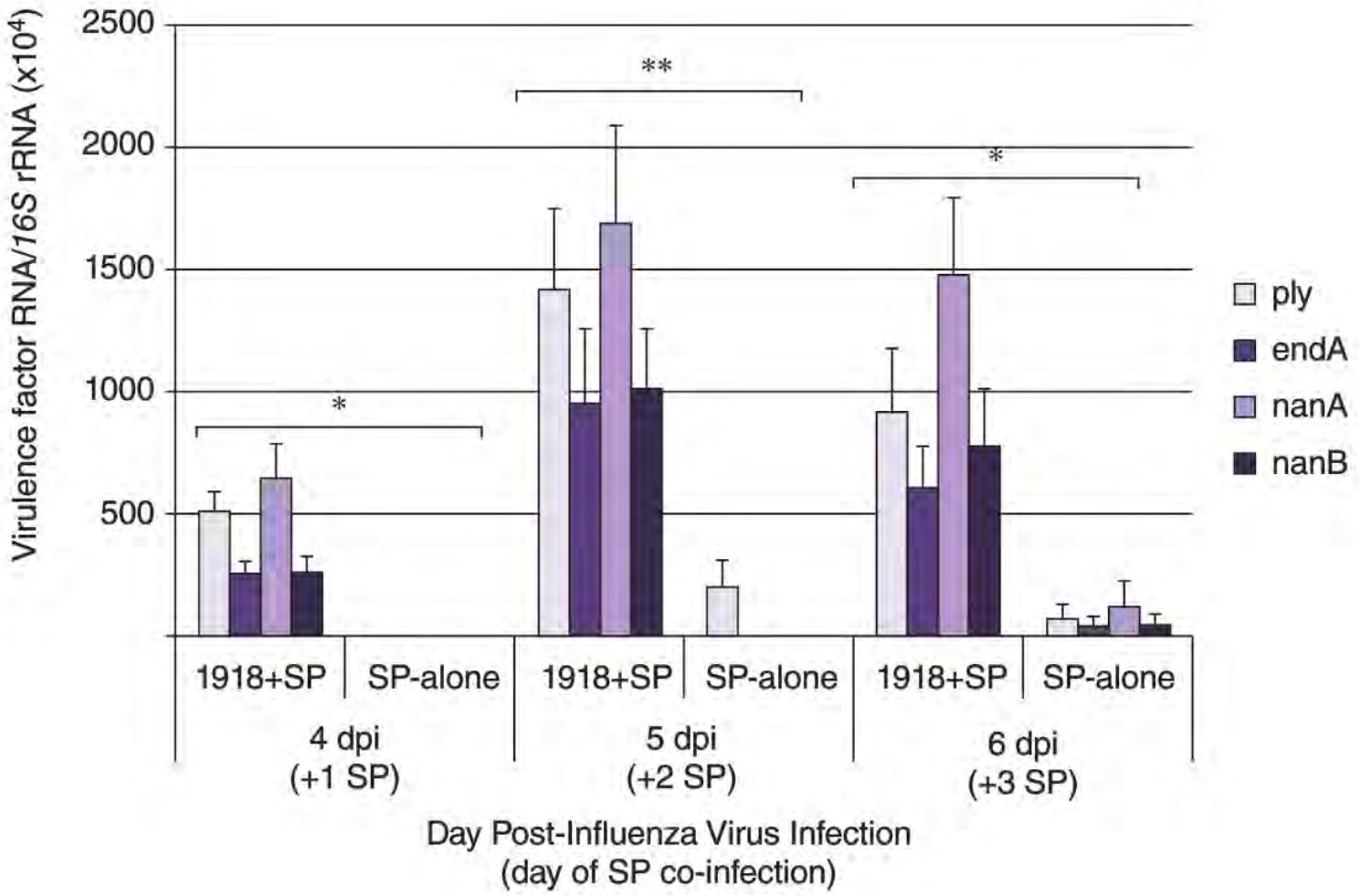


Viral damage to and loss of airway epithelial cells may expose basal epithelial cells to bacteria leading to the death of these progenitor cells, limiting reproliferation

National Institute of Allergy and Infectious Diseases

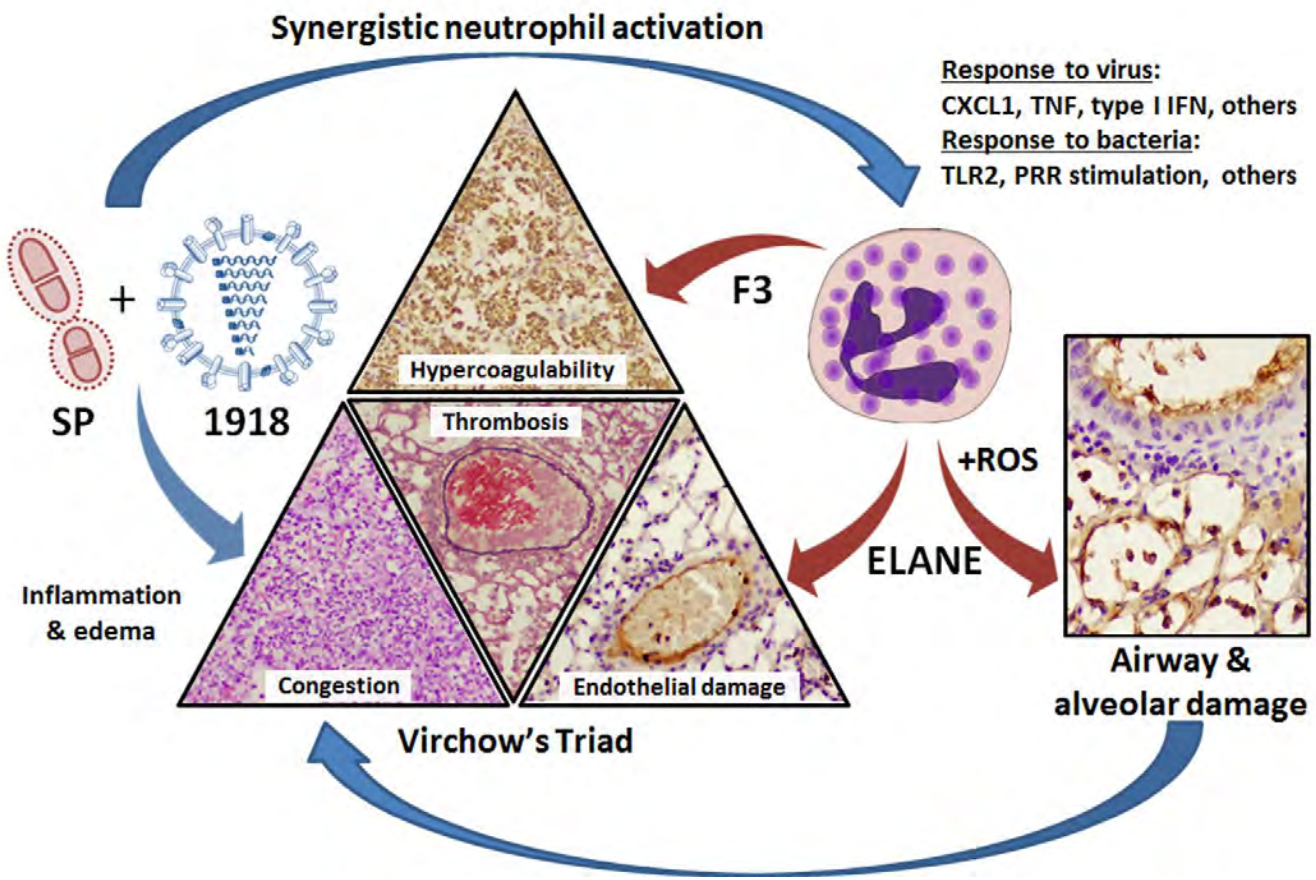
Kash *et al*. 2011 *mBio* 2:e00172

1918 Viral & *Streptococcus pneumoniae* Co-infection alter bacterial gene expression

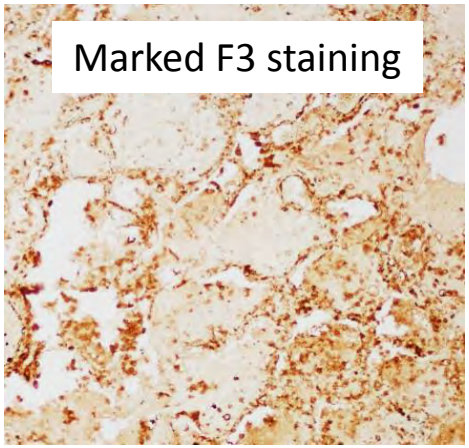


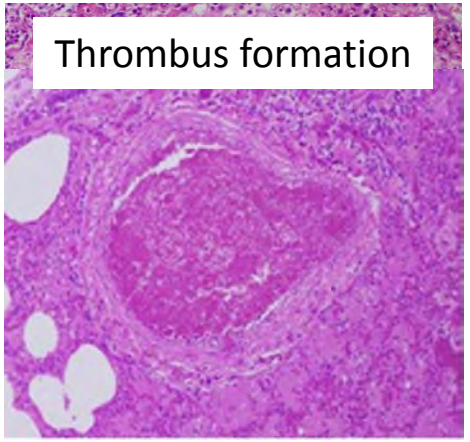
Walters, et al. *J Pathol*. 2016;**238**:85-97

Model of Inflammation and Pulmonary Thrombosis during 1918 & SP Co-Infection



1918 autopsies

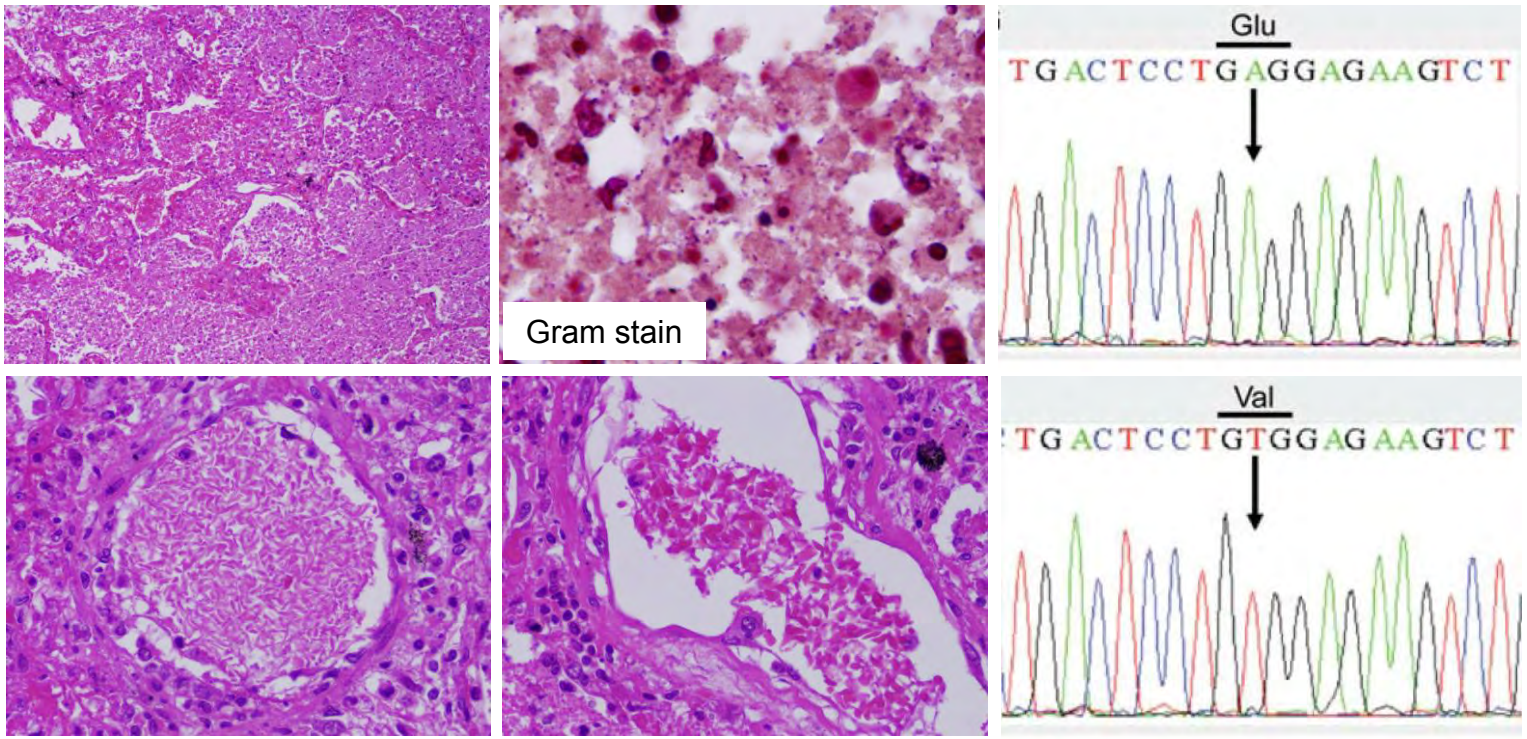




National Institute of Allergy and Infectious Diseases

Walters, et al. *J Pathol*. 2016;**238**:85-97

1918 Pneumonia Case with Prominent Erythrocyte Sickling



DNA sequence of the hemoglobin beta gene from the 1918 FFPE lung tissue showed **Glu6Val hemoglobin S mutation**, 4 years before term "sickle cell anemia" described

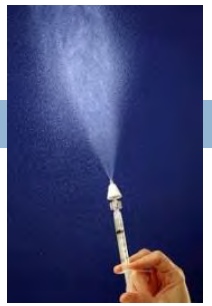
National Institute of Allergy and Infectious Diseases

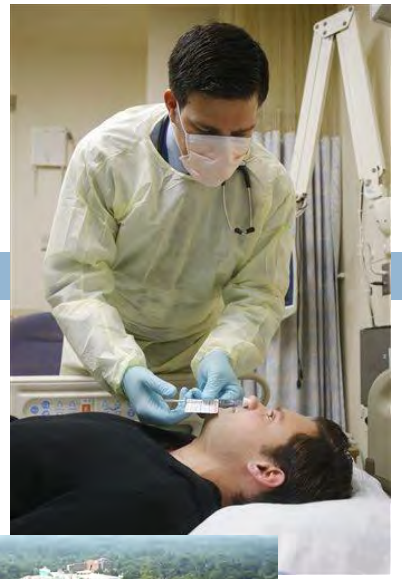
Sheng, *et al*. 2010. EID 16:2000-1

Lessons Learned

- 1918 pathogenesis is multifactorial involving the interplay of viral virulence factors, host inflammatory response, and secondary bacterial infections
- 1918 virulence likely not a pandemic specific mutation but a phenotype observed with influenza viruses expressing certain avian HA subtypes in a mammalian host (H1, H6, H10, H15)
- Future pandemics viruses with one of these subtypes may share features and severity with the 1918 virus
- Future pandemics may be dependent on how long H1N1 and H3N2 viruses circulate

Human Influenza Challenge Studies at NIH Clinical Center





- VPES human influenza challenge model
  - Healthy adult volunteer, in-patient study (min 9 days)
  - GMP-manufactured wild-type IAVs
  - 2009 pandemic H1N1 and 2012 H3N2 IAVs
  - Other challenge viruses in production (H1s, H3s, Bs)
  - >400 participants challenged to date
- Phase I and II challenge studies
  - Basic pathogenesis and correlates of protection
  - Completed vaccine and therapeutic antibody trials
  - VPES universal vaccine candidate Phase I testing in 1 year

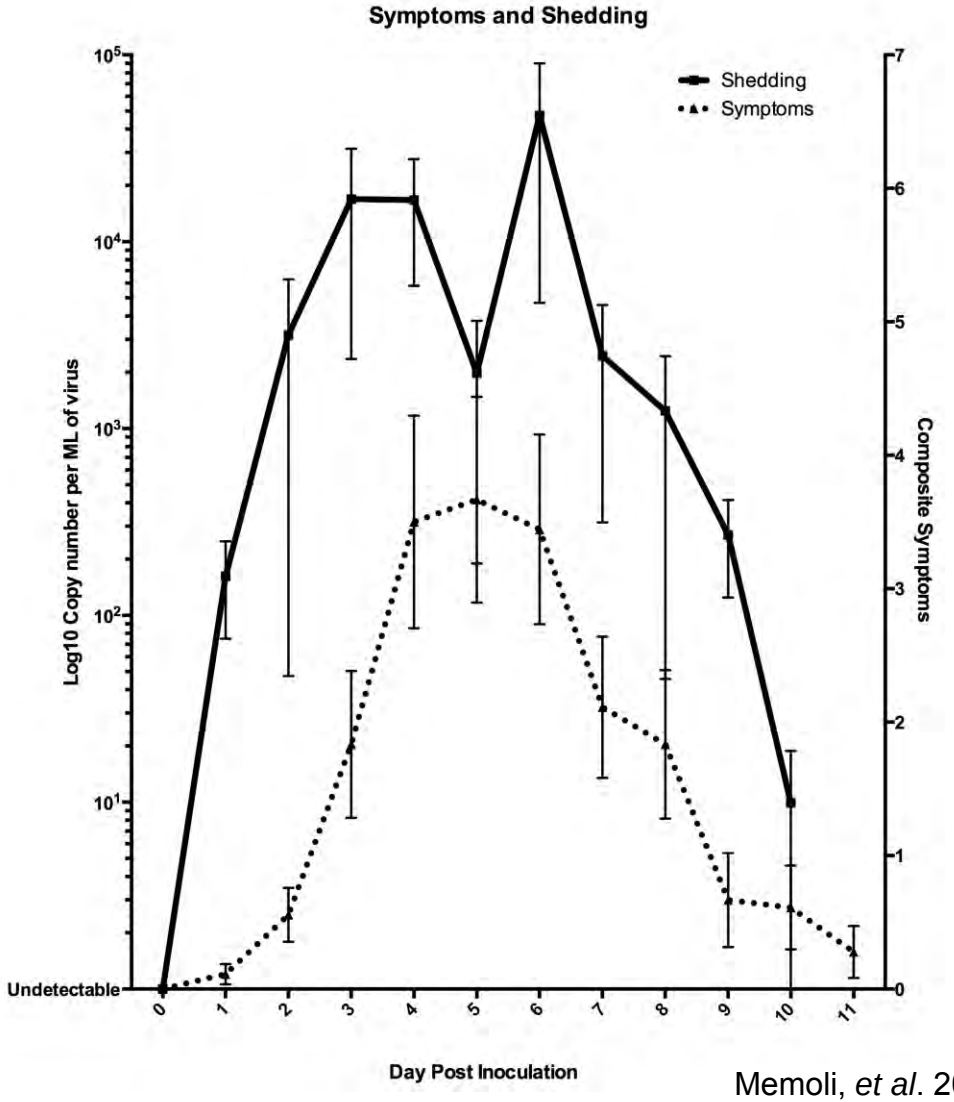
Serologic Correlates of Protection

Binary Endpoints	HAI	NAI	Stalk Titer	
MMID (Shedding + Symptoms)	Yes	Yes	Yes	Reduction in MMID with high titers
Symptoms	No	No	No	No reduction in symptoms
Shedding	Yes	Yes	No	Reduction in +/- shedding

	Linear Correlation			Multiple Regression
Continuous Disease Severity Measures	**HAI**	**NAI**	**Stalk Titer**	**Independent Predictor**
Shedding Duration	Yes	Yes	Yes	NAI, not Stalk or HAI titer
Symptom Duration	Yes	Yes	No	NAI, not Stalk or HAI titer
Number of Symptoms	No	Yes	Yes	NAI, not Stalk or HAI titer
Symptom Severity (FluPRO)	No	Yes	No	NAI, not Stalk or HAI titer

Memoli *et al*. Clin Infect Dis. 2015;60:693-702
Memoli *et al*. mBio. 2016;7:e00417-16
Park *et al*. mBio 2018;9:e02284-17

Influenza Challenge Study – Symptoms and Shedding



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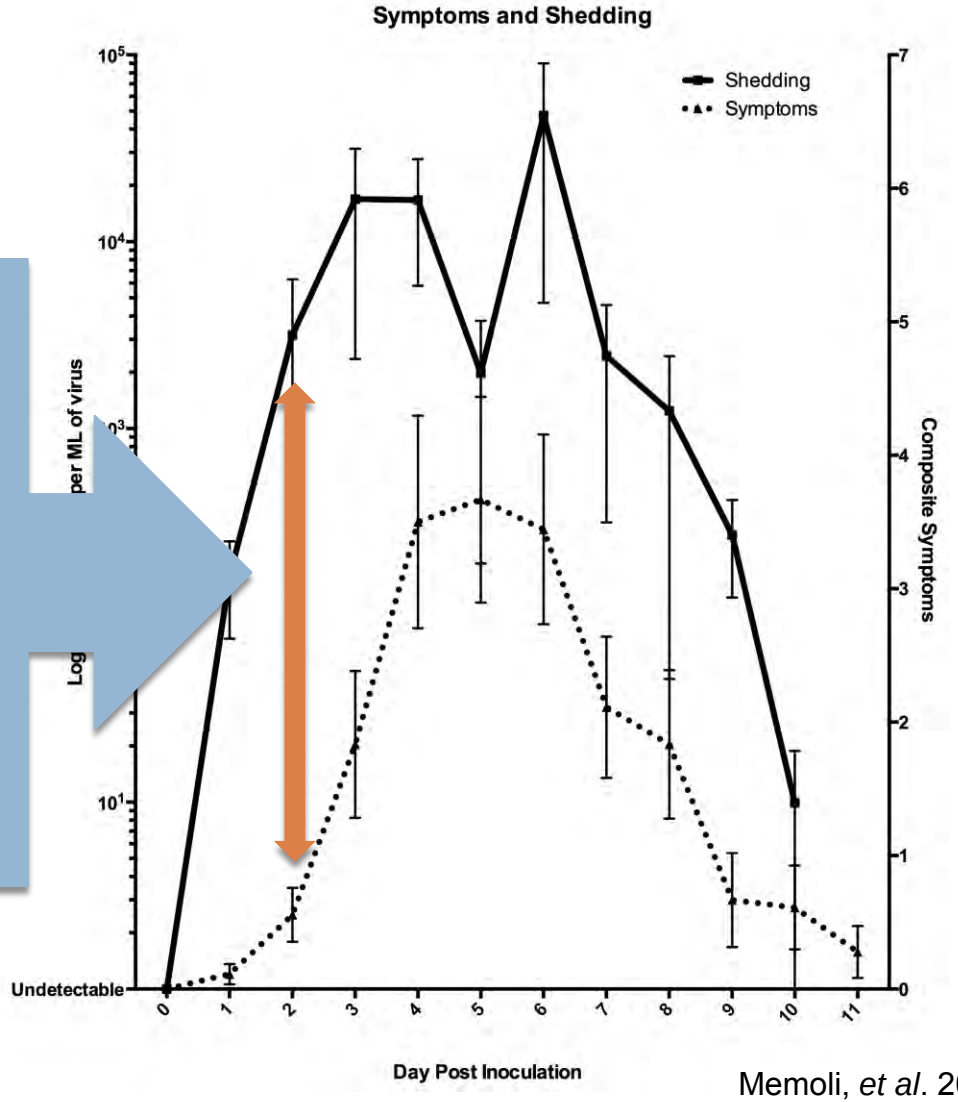
Memoli, *et al*. 2015. Clin Infect Dis. 60:693-702

Influenza Challenge Study – Symptoms and Shedding

Patients shedding 3-4 log_{10} virus on day 2 with very few symptoms



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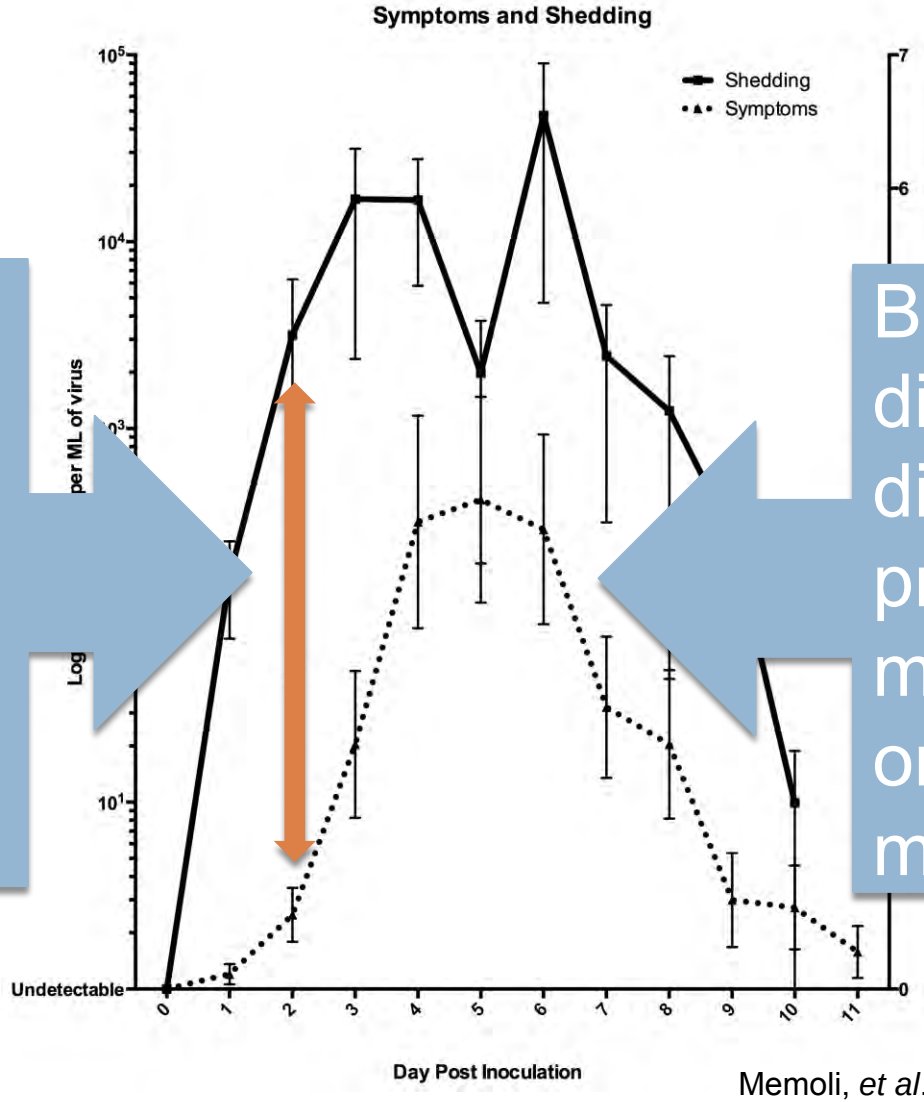
Memoli, *et al*. 2015. Clin Infect Dis. 60:693-702

Influenza Challenge Study – Symptoms and Shedding



Patients shedding 3-4 $\log_{10}$ virus on day 2 with very few symptoms

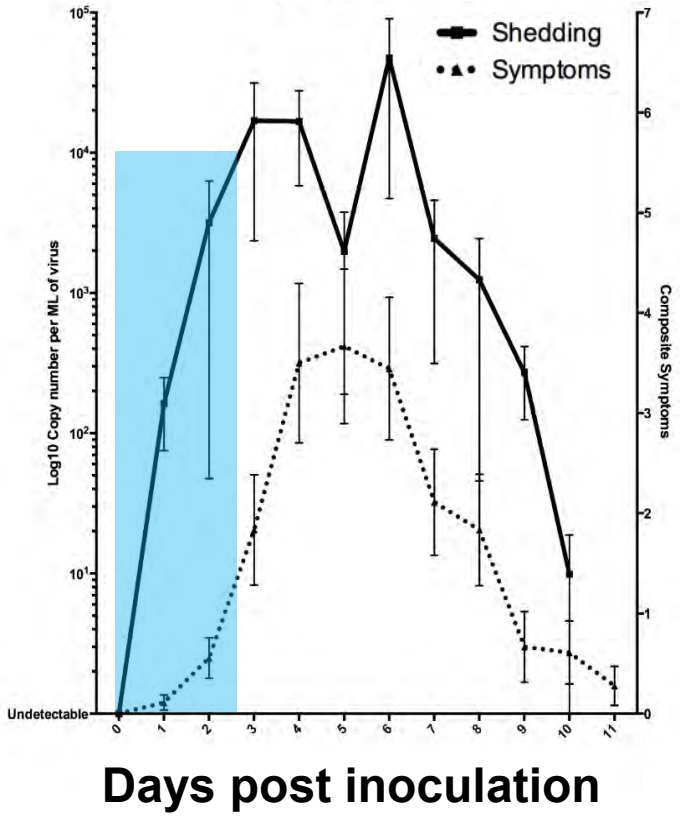
Biomarker discovery: diagnostic and prognostic mRNA, miRNA, or proteomic markers

National Institute of Allergy and Infectious Diseases

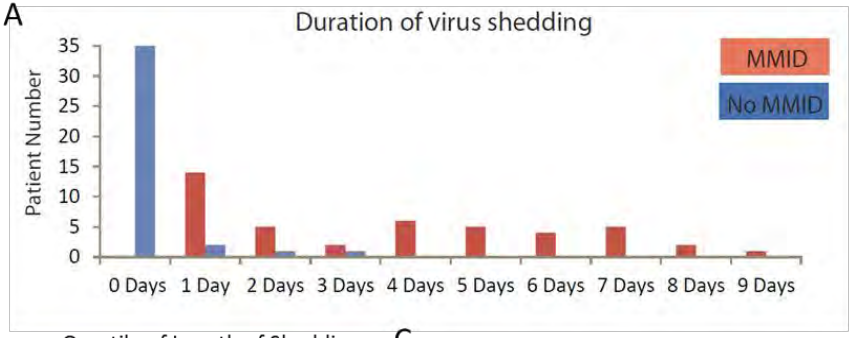
Memoli, *et al*. 2015. Clin Infect Dis. 60:693-702

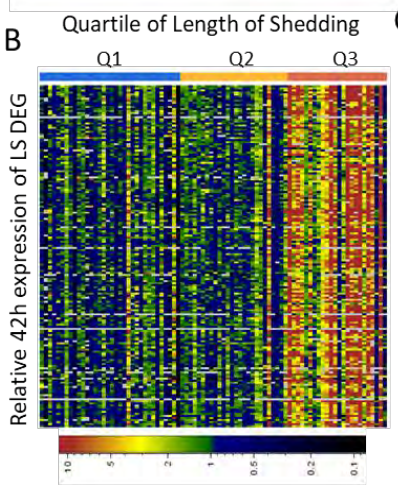
PBL Transcriptome Analysis – Prognostic Biomarker Discovery

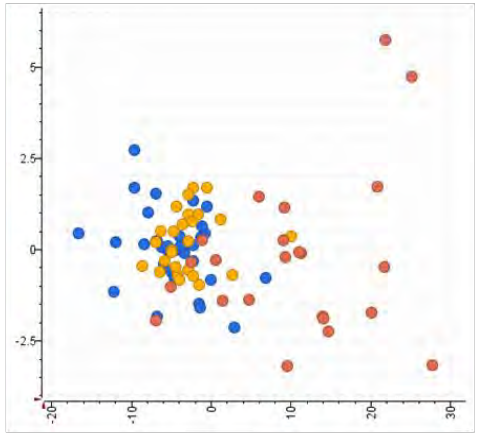
Symptoms and Shedding

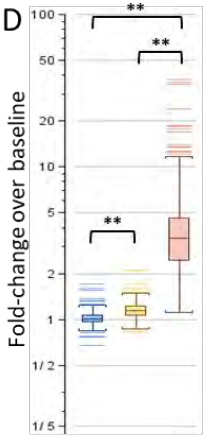


Days post inoculation

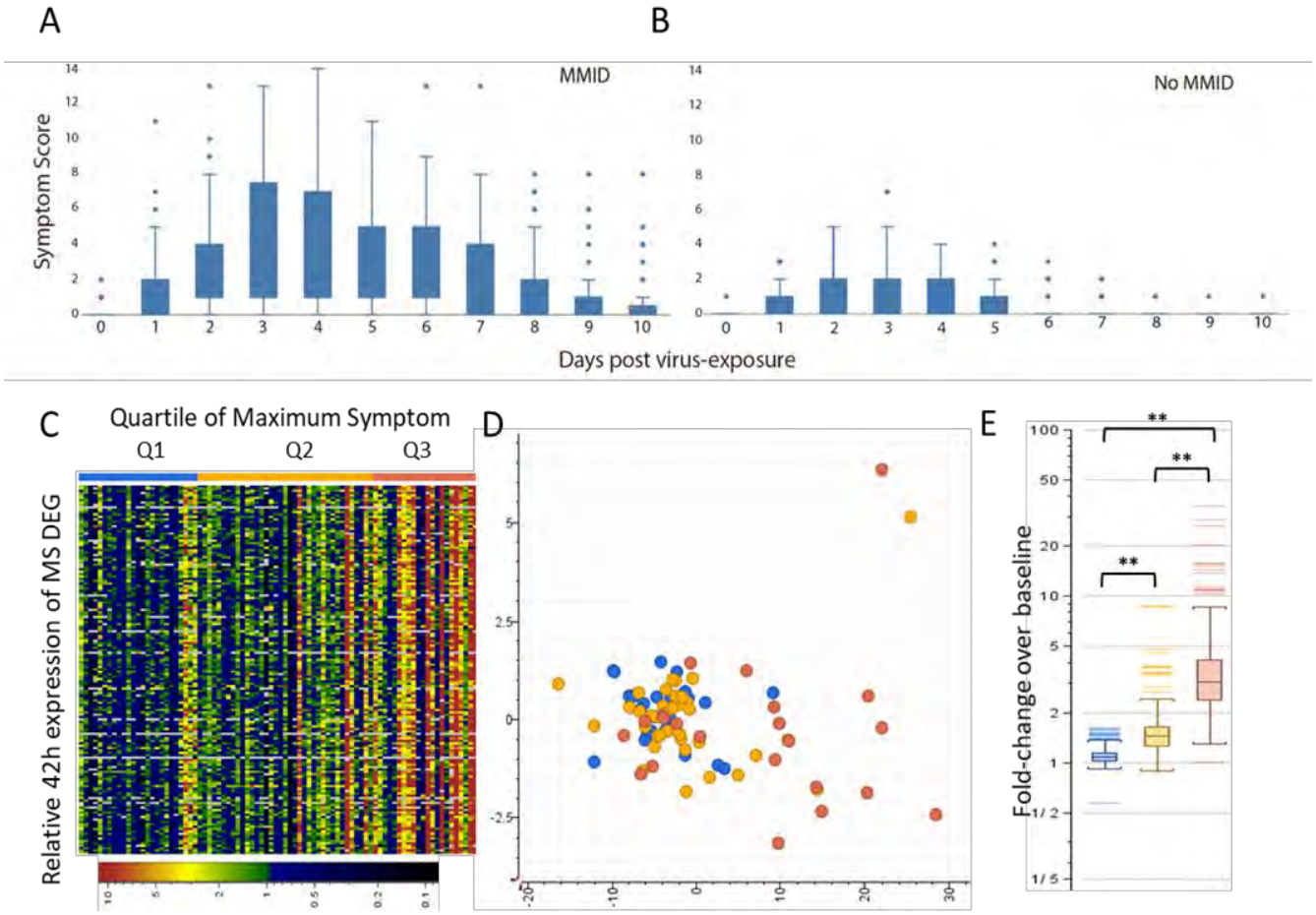








Human PBL Expression of Genes Predicting Illness Severity at D2



Improved Influenza Vaccines

- Universal influenza vaccines could:
  - Offer pre-pandemic protection against all influenza A viruses (H1-H16), or
  - Protect against seasonal viruses, or
  - Protect against both

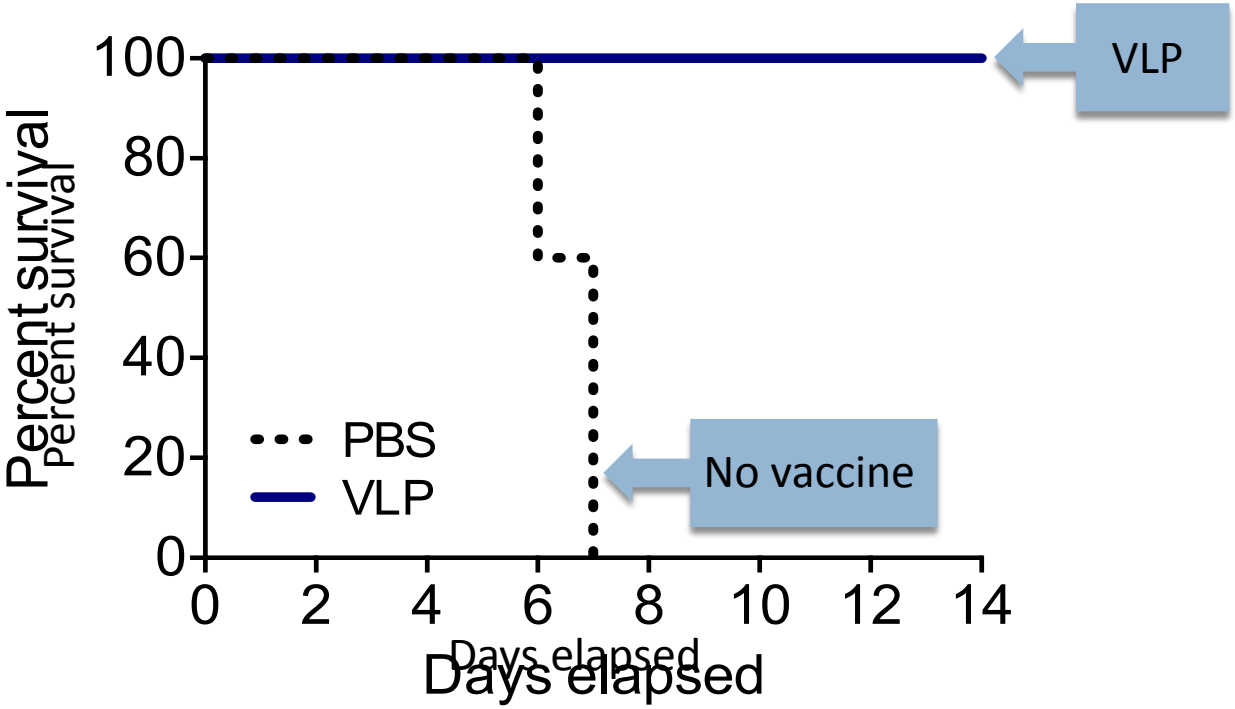
Broadly Protective Influenza Vaccines

- **Concept:** Non-infectious vaccines presenting a mixture of avian influenza hemagglutinins would induce broad cross-protection without need for antigenic matching to specific strains

- **Proof of Concept:** A vaccine cocktail (H1, H3, H5, H7) provides extremely broad cross-protection against most or all influenza A viruses

Experimental Vaccine is Strongly Protective

100% protection against 10x LD_{50} 1918 H1N1
(Intrasubtypic challenge)



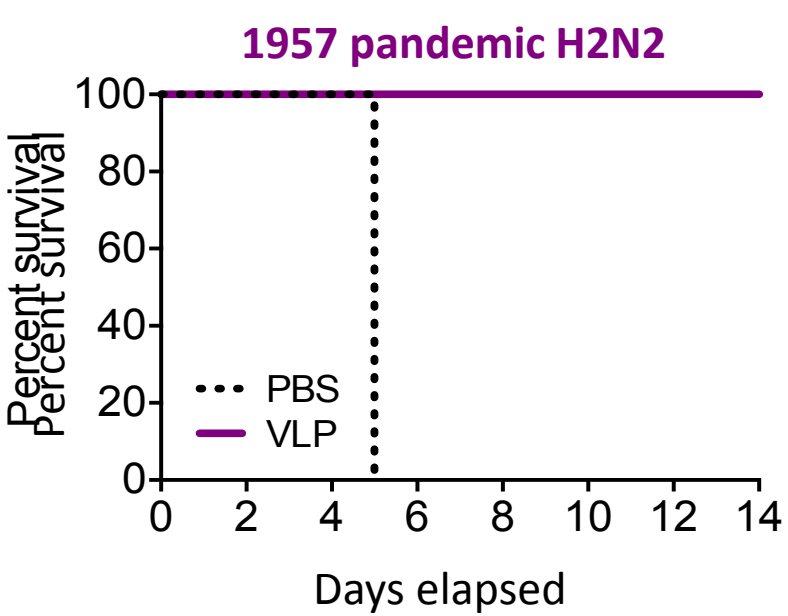
Days elapsed

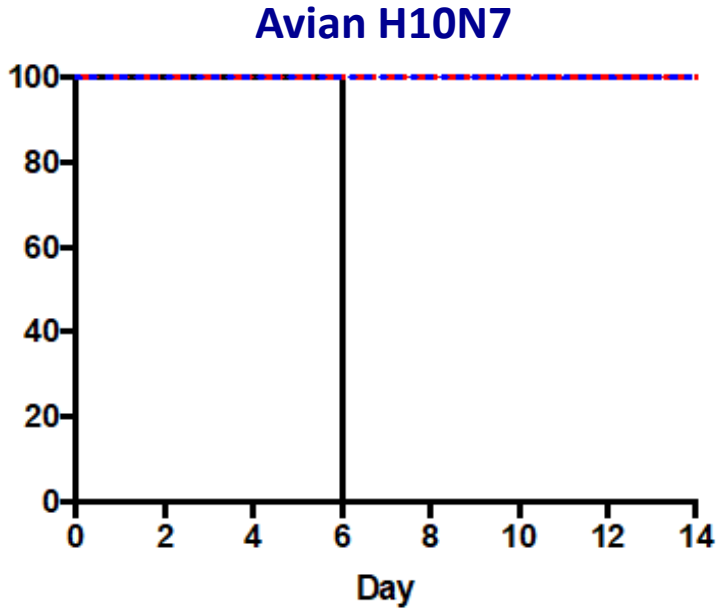
National Institute of Allergy and Infectious Diseases

Schwartzman, *et al*. *mBio*. 2015; **6**:e01044

Experimental Vaccine is Broadly Protective

100% Protection against subtypes ***not*** in the vaccine
(e.g., 10x LD_{50} 1957 H2 pandemic, avian H10, H11, & H15)





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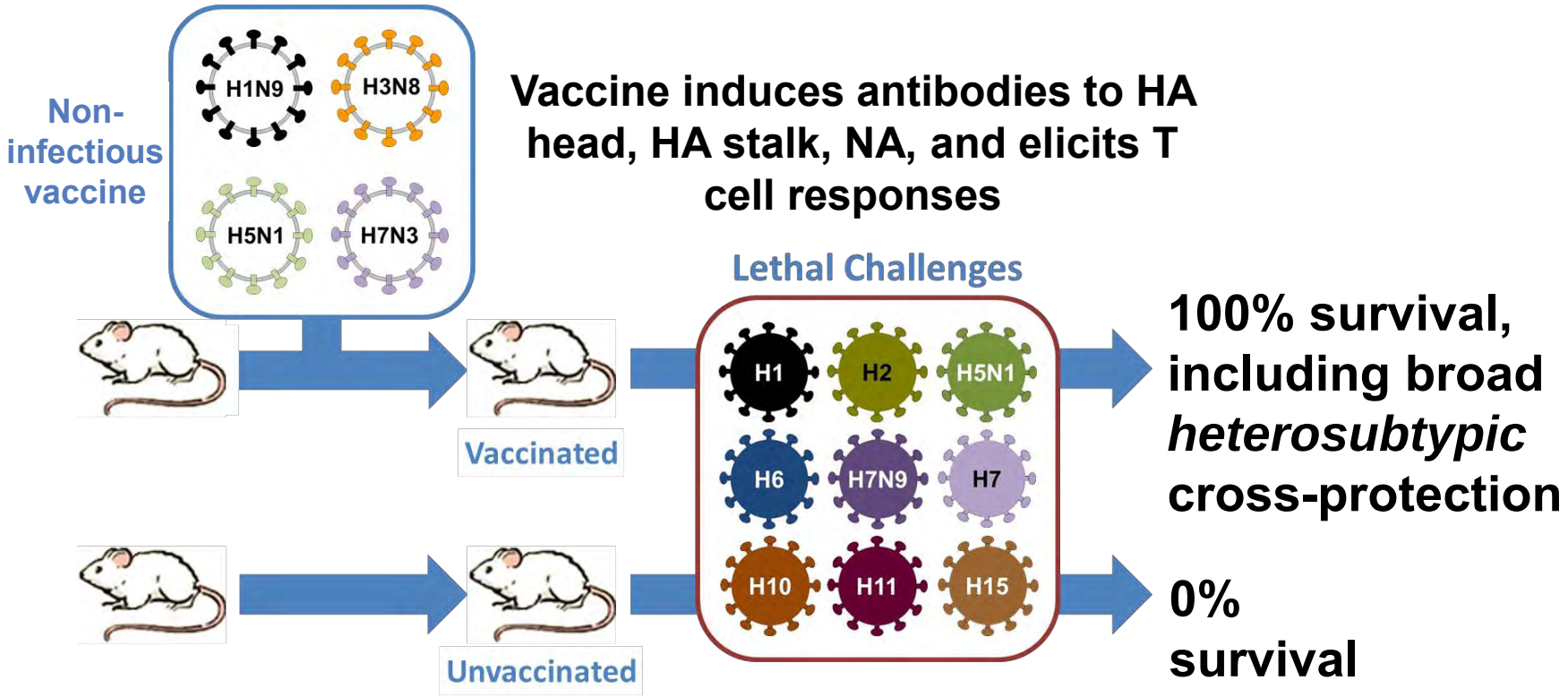
Schwartzman, *et al*. *mBio*. 2015; **6**:e01044

Tetravalent Influenza Vaccine Provides Broad Protection



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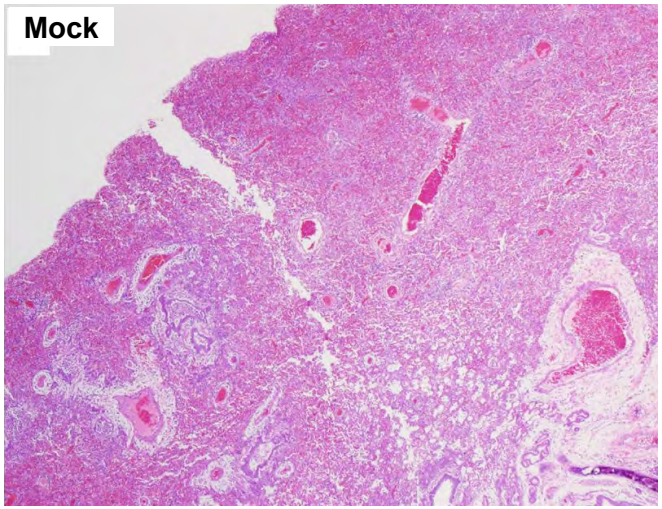
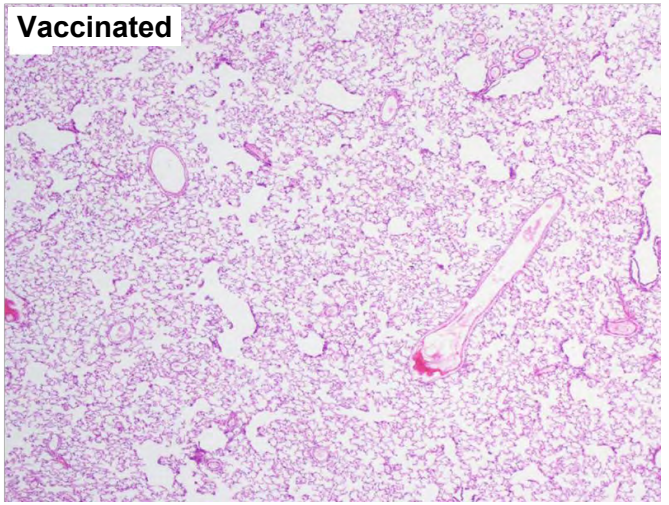
Schwartzman, *et al*. *mBio*. 2015; **6**:e01044
Park, et al. Unpublished

Tetravalent Vaccine Efficacy in Ferrets

- **Challenge with antigenically mismatched H1, H3 viruses**
- **Rapid clearance of virus from nasal and lung tissues**
  10,000-100,000 fold reductions in viral titer
- **Prevention of pneumonia**





Lessons Learned

- Influenza Pathogenicity is a complex of viral, host, and secondary bacterial factors
- 1918 virulence is shared with circulating avian influenza viruses
- Studying viral pathogenesis and host responses in humans is critically needed for rational universal vaccine design
- Influenza challenge models are ideal for detailed studies of immune and molecular correlates of disease and protection and are ideal models to evaluate new vaccines and drugs in phase II trials

The End…?

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